Knobbe Martens Olson & Bear LLP
Intellectual Property Law

2040 Main Street
Fourteenth Floor
Irvine, CA 92614
Tel 949-760-0404
Fax 949-760-9502
www.kmob.com

#18

Mallary K. de Merlier
mdemerlier@kmob.com

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION BY "EXPRESS MAIL"

Attorney Docket No.	:	PCIRA.000GEN
Applicant(s)	:	Sankaram et al.
For	:	MULTIVESICULAR LIPOSOMES WITH CONTROLLED RELEASE OF ENCAPSULATED BIOLOGICALLY ACTIVE SUBSTANCES
Attorney	:	Mallary K. de Merlier
"Express Mail" Label No.	:	EM 572 334 523 US
Date of Deposit	:	December 22, 2011

The following documents are hereby placed into an Express Mail envelope bearing the number indicated above, which envelope is being deposited today with the U.S. Postal Service as Express Mail:

Transmittal letter; Application For Extension Of Patent Term Based On Regulatory Review Of A New Drug Application Pursuant To 35 U.S.C. §156 in 15 pages (original plus two copies); Exhibits A-R (original plus two copies); Fee Transmittal; Check for Filing Fee; Return Prepaid Postcard.

The envelope, with the enclosures listed above, is addressed Mail Stop Hatch-Waxman PTE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

This submission is being made in compliance with 37 CFR 1.10.

Name: _____
Docketing Agent

12475402
122111

Please Direct All Correspondence to Customer Number 59747

TRANSMITTAL LETTER

In re Patent of	:	Sankaram et al..
App. No.	:	09/045,236
Filed	:	March 20, 1998
Patent No.		6,132,766
Issued	:	October 17, 2000
For	:	MULTIVESICULAR LIPOSOMES WITH CONTROLLED RELEASE OF ENCAPSULATED BIOLOGICALLY ACTIVE SUBSTANCES

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed are the following items for filing in connection with the above-referenced Patent Application:

(X) Fee Transmittal;

(X) Request for Extension of Patent Term under 35 U.S.C. § 156 (original plus two copies) together with Exhibits A-R (original plus two copies);

(X) A check in the amount of $1,120.00; and

(X) Return receipt postcard.

The Commissioner is hereby authorized to charge any additional fees which may be required, now or in the future, including fees for extension of time, or credit any overpayment, to Account No. 11-1410.

Mallary K. de Merlier
Registration No. 51,609
Attorney of Record
Customer No. 20,995
(858) 707-4000

12475657
122111

PTO/SB/17 (09-11)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number

FEE TRANSMITTAL

Complete if Known	
Application Number	09/045,236
Filing Date	March 20, 1998
First Named Inventor	Sankaram, et al
Examiner Name	N/A
Art Unit	N/A
Attorney Docket No.	PCIRA.000GEN

RECEIVED
DEC 22 2011
PATENT EXTENSION
OPLA

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120.00

METHOD OF PAYMENT (check all that apply)

☑ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☐ Deposit Account Deposit Account Number: 11-1410 Deposit Account Name: Knobbe Martens

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☐ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	380	190	620	310	250	125	
Design	250	125	120	60	160	80	
Plant	250	125	380	190	200	100	
Reissue	380	190	620	310	750	375	
Provisional	250	125	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	60	30
Each independent claim over 3 (including Reissues)	250	125
Multiple dependent claims	450	225

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 20 or HP =	_____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 3 or HP =	_____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 =	_____	/ 50 = _____ (round up to a whole number)	x _____	= _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): 1457 Extension of term of patent	1,120.00

SUBMITTED BY

Signature	Mallary de Merlier	Registration No. (Attorney/Agent) 51609	Telephone (858) 707-4000
Name (Print/Type)	Mallary K. de Merlier		Date December 22, 2011

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of	:	Sankaram et al.
App. No	:	09/045,236
Filed:	:	March 20, 1998
Patent No.:		6,132,766
Issued:		October 17, 2000
For	:	MULTIVESICULAR LIPOSOMES WITH CONTROLLED RELEASE OF ENCAPSULATED BIOLOGICALLY ACTIVE SUBSTANCES

CERTIFICATE OF EXPRESS MAILING

Express Mail Label No. EM 572334523 US

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service by express mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

December 22, 2011
(Date)

Mallary K. de Merlier, Reg. No. 51,609

APPLICATION FOR EXTENSION OF PATENT TERM BASED ON REGULATORY REVIEW OF A NEW DRUG APPLICATION PURSUANT TO 35 U.S.C. §156

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

RECEIVED
DEC 22 2011
PATENT EXTENSION
OPLA

Dear Sir:

The Applicant, Pacira Pharmaceuticals, Inc., of 10450 Science Center Drive San Diego, CA 92121, represents that it is the owner of record of the entire right, title and interest in and to U. S. Patent No. 6,132,766 (the '766 Patent), as evidenced by the Assignments from the inventors, Mantripragada Bhima Sankaram and Sinil Kim to DepoTech Corporation, recorded on September 11, 1995 under Reel/Frame: 7762/0186. DepoTech Corporation merged with SkyePharma, Inc. and the merger documents were recorded on August 2, 1999 under Reel/Frame: 010121/0893. SkyePharma, Inc. changed its name to Pacira Pharmaceuticals and the name change documents were recorded on February 21, 2008 at Reel/Frame: 020550/0289. Copies of the recorded Assignment, corporate merger and name change documents are submitted as **Exhibit A**.

The '766 Patent matured from United States Patent Application No. 09/045,236, filed on March 20, 1998, which is a division of U.S. Application No. 08/473,013, filed on June 6, 1995,

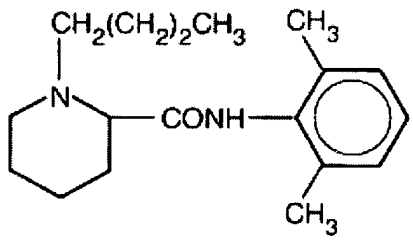
now abandoned, which is a continuation of Application No. 08/153,657, filed on November 16, 1993, now abandoned.

This application for patent term extension is based on the regulatory approval of EXPAREL™ , a bupivacaine liposome injectable suspension, referred to herein as "EXPAREL" or "Approved Product." The active ingredient in EXPAREL is bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia.

Pacira Pharmaceuticals, Inc. hereby applies, pursuant to 35 U.S.C. § 156(d) (1) and 37 C.F.R. § 1.740, for extension of the term of the above-identified U.S. Patent No. 6,132,766. The patent term extension is requested until March 28, 2017, 1,228 days from the original expiration date, or such greater or lesser period as the Commissioner may deem Pacira Pharmaceuticals, Inc. to be entitled. The following information follows the numerical format set forth in 37 C.F.R. § 1.740:

1. ***A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:***

Pacira Pharmaceuticals, Inc. submits herewith as **Exhibit B** to this application the prescribing information for EXPAREL™ as approved by the U.S. Food and Drug Administration (FDA). EXPAREL™ is a multivesicular liposome injection of bupivacaine, an amide local anesthetic, indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia. Chemically, bupivacaine is 1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxyamide with a molecular weight of 288.4. The structure of bupivacaine is:



2. ***A complete identification of the Federal statute, including the applicable provision of law under which the regulatory review occurred.***

The regulatory review was conducted under Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act (FFDCA) (21 U.S.C. § 355).

3. ***An identification of the date on which the product received permission for applicable regulatory review period occurred:***

The Approved Product received permission for commercial marketing or use by the United States Food and Drug Administration (FDA) pursuant to section 505 (b)(2) of the FFDCA in a letter dated October 28, 2011. A copy of the approval letter is attached as **Exhibit C.**

4. ***An identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.***

As stated above, the Approved Product is an injectable liposome comprising bupivacaine as the active ingredient. A bupivacaine liposome injectable suspension has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act.

Bupivacaine hydrochloride as an injectable was approved under the proprietary name MARCAINE HYDROCHLORIDE under Application No. N016964 prior to January 1, 1982, according to the Orange Book listing of approved drug products. Bupivacaine hydrochloride and epinephrine bitartrate were approved prior to January 1, 1982. Bupivacaine hydrochloride as an injectable was approved under Application No. N018053 prior to January 1, 1982. Bupivacaine hydrochloride as a spinal injectable under the proprietary name MARCAINE was approved under Application Number N018692 on May 4, 1984. Bupivacaine hydrochloride and epinephrine

bitartrate were approved as an injectable under Application Number N022046 on July 13, 1983. See **Exhibit D**. It is believed that bupivacaine was approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or non-lipid –associated drug. Applicant submits that bupivacaine as a liposomal injectable is a different "product" with a different "active ingredient" as the terms are used in § 156 of the FFDCA. A bupivacaine liposome injectable suspension warrants separate patenting and separate regulatory approval. Accordingly, Applicant submits a bupivacaine liposome injectable suspension as a "product" has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act.

5. ***A statement that the application is being submitted within the sixty day period permitted for submission pursuant to Section 1.720(f) and an identification of the date of the last day on which the application could be submitted:***

This Application is being submitted on or before December 27, 2011, the last day of the sixty-day period permitted for submission pursuant to 37 C.F.R. § 1.720(f), i.e. the last day of the sixty-day period following the October 28, 2011 approval for commercial marketing of EXPAREL™.

6. ***A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:***

This Application seeks extension for U.S. Patent No. 6,132,766, issued to Mantripragada Bhima Sankaram and Sinil Kim on October 17, 2000. The patent will expire on November 16, 2013.

7. ***A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.***

A copy of U.S. Patent No. 6,132,766, including claims and drawings, is enclosed as **Exhibit E.**

8. ***A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:***

Copies of the Terminal Disclaimer are enclosed as **Exhibit F**. A copy of the Certificate of Correction is enclosed as **Exhibit G.** Copies of the Maintenance Fee Statements are enclosed as **Exhibit H.** U.S. Patent No. 6,132,766 has not been subject to any reexamination.

9. ***A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or method of using or manufacturing the approved product.***

U.S. Patent No. 6,132,766 claims a multivesicular liposome composition containing a biologically active substance. The approved product, as described above, is a sterile, non-pyrogenic white to off-white preservative-free aqueous suspension of multivesicular liposomes (DepoFoam® drug delivery system) containing bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce post-surgical analgesia. See Product Insert attached as **Exhibit I.** At least Claim 1 and Claim 4 of U.S. Patent No. 6,132,766 relate to the approved product and the process for obtaining the approved product. These claims are set forth below:

> Claim 1. A multivesicular liposome having multiple non-concentric chambers with internal membranes distributed as a network throughout, produced by a method comprising the steps of:
>
> (a) forming a water-in-oil emulsion from two immiscible components, the two immiscible components being:

1) a lipid component comprising at least one organic solvent, at least one amphipathic lipid, and at least one neutral lipid lacking a hydrophilic head group, and

2) a first aqueous component;

said water-in-oil emulsion further comprising:

3) non-hydrohalic acid in a concentration range from about 0.1 mM to about 0.5 M, wherein the concentration is selected to provide controlled release of the biologically active substance in 4) from the liposome, and

4) at least one biologically active substance;

said non-hydrohalic acid and said biologically active substance being independently incorporated into the lipid component, the first aqueous component, or both;

(b) mixing the water-in-oil emulsion containing the non-hydrohalic acid with a second aqueous component to form solvent spherules; and thereafter

c) removing the organic solvent from the solvent spherules to form multivesicular liposomes.

Claim 4: The liposome of claim 1, wherein the biologically active agent is selected from the group consisting of an antitumor agent, an anaesthetic, an analgesic, an antimicrobial agent, a hormone, an antiasthmatic agent, a cardiac glycoside, an antihypertensive, a vaccine, an antiarrhythmic, an immunomodulator, a steroid, a monoclonal antibody, a neurotransmitter, a radionuclide, a radio contrast agent, a nucleic acid, a protein, a herbicide, a pesticide, and suitable combinations thereof.

Pursuant to 37 C.F.R. §1.740(a)(9), a showing which demonstrates the manner in which one claim reads on the Approved Product is set forth herein below:

Claim 1. 1. A multivesicular liposome having multiple non-concentric chambers with internal membranes distributed as a network throughout, produced by a method comprising the steps of: (a) forming a water-in-oil emulsion from two immiscible components, the two immiscible components being: 1) a lipid component comprising at least one organic solvent, at least one amphipathic lipid, and at least one neutral lipid lacking a hydrophilic head group, and 2) a first aqueous component; said water-in-oil emulsion further comprising:3) non-hydrohalic acid in a concentration range from about 0.1 mM to about 0.5 M, wherein the concentration is	**Approved product:** As shown in the approved labeling (attached as **Exhibit I**) EXPAREL™ (multivesicular liposome injection of bupivacaine) was approved for single-dose administration into the surgical site to produce post-surgical analgesia. Each vial contains the biologically active substance of bupivacaine at a nominal concentration of 13.3 mg/mL, incorporated in a multivesicular liposome formed by the process set forth in Claim 1 of the '766 Patent.

selected to provide controlled release of the biologically active substance in 4) from the liposome, and 4) at least one biologically active substance; said non-hydrohalic acid and said biologically active substance being independently incorporated into the lipid component, the first aqueous component, or both; (b) mixing the water-in-oil emulsion containing the non-hydrohalic acid with a second aqueous component to form solvent spherules; and thereafter (c) removing the organic solvent from the solvent spherules to form multivesicular liposomes.	

10. ***A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:***

    (i) for a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued.

The following dates and related information are applicable for the new drug application (NDA) approval of EXPAREL™:

Date of original IND	:	December 9, 2004	**(Exhibit J)**
IND Number	:	69,198	
Request for Inactivation of IND 69,198	:	January 6, 2005	**(Exhibit K)**
Date of Inactivation of IND 69,198	:	January 18, 2005	**(Exhibit L)**
Date of Request for Reactivation of IND 69,198	:	March 7, 2006	**(Exhibit M)**
Reactivation of IND 69,198	:	November 13, 2006	**(Exhibit N)**
Submission Date of NDA	:	September 28, 2010 (Cover letter attached as **Exhibit O**).	
FDA Approval Date for NDA	:	October 28, 2011	
NDA Number	:	22-496	

An original investigational new drug application ("IND") was requested by SkyePharma, Inc. on December 9, 2004. The FDA assigned IND No. 69,198. On January 6, 2005, Applicant filed a request for inactivation of IND 69,198 and the FDA acknowledged receipt of same on January 18, 2005. On March 7, 2006, Applicant filed a request for reactivation of IND 69,198. On November 13, 2006, the FDA reactivated IND 69,198.

11. ***A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.***

In accordance with 37 C.F.R. § 1.740(a)(11), a list of significant activities, undertaken by the Marketing Applicant, its predecessors, and affiliates, in IND No. 69,198 and NDA 22-496 during the applicable regulatory review period with respect to the approved product is provided, respectively, at **Exhibits P** and **Q.**

12. ***A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.***

Pacira Pharmaceuticals, Inc. believes that it is entitled to an extension of term for U.S. Patent No. 6,132,766 (the Patent) in accordance with the provisions of 35 U.S.C. § 156. Pacira Pharmaceuticals, Inc. believes that the period of extension applicable to the patent is 1,228 days, based on the following calculation in accordance with 37 C.F.R. § 1.775 (subsections listed below):

(a) Statement of the eligibility of the patent for extension under 35 U.S.C. § 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (i) the term of the patent has not expired before an application for extension is submitted; (ii) the term of the patent has never been extended under 35 U.S.C. § 156(e)(1); (iii) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. § 156(d); (iv) the product has been subject to a regulatory review period before its commercial marketing or use; and (v) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(i) Pursuant to 35 U.S.C. § 154, the term of U.S. Patent No. 6,132,766 is set to expire November 16, 2013. This application is, therefore, being submitted prior to the expiration of the term of U.S. Patent No. 6,132,766.

(ii) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(iii) This application is being submitted by Pacira Pharmaceuticals, Inc., the owner of record of U.S. Patent No. 6,132,766 (See **Exhibit A**). This application is being submitted within the sixty-day period beginning on October 28, 2011, the date the product received permission for marketing under Section 505 of the FFDCA [21 U.S.C. §355], and ending on December 27, 2011. Moreover, this application contains the information required under 35 U.S.C. §156(d).

(iv) As evidenced by the October 28, 2011 letter from the FDA to Pacira Pharmaceuticals, Inc. (**Exhibit C**), the product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(v) The permission for the commercial marketing of EXPAREL™ (bupivacaine liposome injectable suspension) product is the first permitted commercial marketing and use under 35 U.S.C. §156(f). (See, e.g., Section (4), above).

(b) ***Statement as to length of extension claimed.***

The term of U.S. Patent No. 6,132,766, should be extended to March 28, 2017, or 1,228 days from the original expiration date in accordance with 35 U.S.C. § 156.

(c) The length of the regulatory review period for the approved product is calculated as the sum of:

(1) The number of days in the period beginning on the date of exemption under 35 U.S.C. § 156(g)(1)(B)(i) from March 7, 2006 (the presumptive effective date of the IND as the date the IND reactivation request was sent to the FDA) until September 28, 2010 (the NDA submission date) which is 1,666 days; and

(2) The number of days in the review period under 35 U.S.C. §156(g)(1)(B)(i) from September 28, 2010 (the NDA submission date) until October 28, 2011 (marketing approval date), which is 395 days.

Thus, the total regulatory review period under 37 C.F.R. § 1.775 (c) is 2,061 days.

(d) The term is determined as follows:

(1) The sum of the following is subtracted from the regulatory review period (2,061 days) as determined above:

(i) The number of days in the regulatory review period which were on or before the date on which the Patent issued. As the regulatory review commenced after the Patent issued, the number of days is 0 days.

(ii) The number of days in the regulatory review period wherein the Applicant did not act with due diligence, which is 0 days.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) (1666 days) that has been reduced in accordance with the two items above, which is 1,666 divided by 2 = 833 days.

Thus, the term under subsection (d) is 2,061 – 833 = 1,228 days.

(2) The date of expiration of the patent is extended by adding the number of days determined in (d)(1) (1228 days) to the original term of the patent , i.e., November 16, 2013 plus 1,228 days, or March 28, 2017.

(3) Add 14 years to the date of approval (October 28, 2011), which would be October 28, 2025.

(4) Compare the dates of expiration obtained under paragraph (d)(2) and (d)(3) above and select the earlier date. Accordingly, March 28, 2017 is earlier than October 28, 2025.

(5) U.S. Patent No. 6,132,766 issued on October 17, 2000, which is after September 24, 1984. Accordingly paragraph (5) is applicable.

(i) Add 5 years to the date of expiration of the patent (November 16, 2013), which would be November 16, 2018.

(ii) Compare the dates of expiration obtained under paragraphs (d)(4) and (d)(5)(i) above and select the earlier date. Accordingly, March 28, 2017 is earlier than November 16, 2018.

Thus, an extension to March 28, 2017 from the original date of expiration of November 16, 2013 is the maximum allowable extension available to EXPAREL™ on U.S. Patent No. 6,132,766 under 37 C.F.R. §1.775.

13. ***A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (37 C.F.R. §1.765)***

Pacira Pharmaceuticals, Inc. acknowledges a duty to disclose to the Commissioner of Patents and Trademarks (and to the Patent and Trademark Office), and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

14. ***The prescribed fee for receiving and acting upon the application for extension (37 C.F.R. § 1.20(j)).***

Pacira Pharmaceuticals, Inc. hereby encloses a check in the amount of $1,120.00, the prescribed fee under 37 C.F.R. §1.20(j). If for any reason this payment is insufficient, applicant hereby authorizes that any deficiency may be charged, or any overpayment credited, to Deposit Account No. 11-1410.

15. ***The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.***

Please direct all correspondence relating to this application to:

Mallary K. de Merlier
Registration No. 51,609
Attorney of Record
KNOBBE, MARTENS, OLSON & BEAR, LLP
12790 El Camino Real
San Diego, CA 92130
Telephone: (858) 707-4000
Direct Line: (858) 707-4189
Facsimile: (858) 707-4001
E-mail: mdemerlier@kmob.com

16. ***A duplicate of the application papers, certified as such.***

Pacira Pharmaceuticals, Inc. hereby certifies that this application for patent term extension and supporting papers is being filed in triplicate (the original plus two copies), and certifies that the copies are true copies of the original application and supporting papers.

17. ***An oath or declaration***

A Declaration as set forth in 37 C.F.R. §1.740(b) accompanies the present Application as **Exhibit R.**

If this application for extension of patent term is held to be informal, Pacira Pharmaceuticals, Inc. may seek to have the holding reviewed by filing a petition with the required fee, as necessary, pursuant to 37 C.F.R. § 1.181 or 1.183, as appropriate, within such time as may be set in any notice that the application has been held to be informal, or if no time is set, within one month of the date on which the application was held informal.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: December 22, 2011

By: _____

Mallary K. de Merlier
Registration No. 51,609
Attorney of Record
Customer No. 20,995
(858) 707-4000

12418873
121211
12475230
122111

EXHIBIT A

'Substitute Form PTO-1595

40:(8) 581 AM

Attorney Docket No.: 07333/022001

RECORDATION FORM COVER SHEET
PATENTS ONLY

MRD 9-11-95

71638 U.S. PTO

[redacted]

01/05/96

Commissioner of Patents and Trademarks: Please record the attached original document.

1. Name of conveying party(ies):
Mantripragada Bhima Sankaram
Sinil Kim

Additional name(s) attached? ☐ Yes ■ No

2. Name and address of receiving party(ies):
DepoTech Corporation
11025 North Torrey Pines Road
Suite 100
La Jolla, California 92037

Additional names/addresses attached? ☐ Yes ■ No

3. Nature of conveyance:
- ■ Assignment
- ☐ Merger
- ☐ Security Agreement
- ☐ Change of Name
- ☐ Other:

Execution Date:
July 3, 1995

01-25-1996

[redacted]

100120398

4. Application number(s) or patent number(s):
If this document is being filed with a new application, the execution date of the application is:

A. Patent Application No.(s):
08/473,013

B. Patent No.(s):

Additional numbers attached? ☐ Yes ■ No

5. Name/address of party to whom correspondence concerning document should be mailed:

June M. Learn
Fish & Richardson P.C.
4225 Executive Square, Suite 1400
La Jolla, CA 92037

6. Total number of applications/patents involved: one

7. Total fee (37 CFR 3.41): **$40**
■ Enclosed
☐ Authorized to charge deposit account

8. Deposit account number: **06-1050**
If the fee above is being charged to deposit account, a duplicate copy of this cover sheet is attached. Please apply any additional charges, or any credits, to our Deposit Account No. 06-1050.

DO NOT USE THIS SPACE

9. Statement and signature: *To the best of my knowledge and belief, the foregoing information is true and correct and the attached is the original document.*

Susan M. Regan	Susan M. Regan	September 5, 1995
Name of Person Signing	Signature	Date

Total number of pages including cover sheet, attachments, and document: 2

250 BB 09/20/95 08473013
1 581 40.00 CK

07333/022001
(CIP of PD3177)

ASSIGNMENT

For valuable consideration, we, Mantripragada Bhima Sarkaram and Sinil Kim of San Diego, California and Solana Beach, California, respectively, hereby assign to DepoTech Corporation, a California Corporation having a place of business at 11025 North Torrey Pines Road, Suite 100, La Jolla, California 92037, its successors and assigns (collectively hereinafter called "the Assignee"), the entire right, title and interest throughout the world in the inventions and improvements which are subject of an application for United States Patent signed by us this day, entitled MULTIVESICULAR LIPOSOMES WITH CONTROLLED RELEASE OF ENCAPSULATED BIOLOGICALLY ACTIVE SUBSTANCES, filed 6/6/95, Serial No. _____ (Continuation-in-Part of U.S. Serial No. 08/153,657, filed November 16, 1993);

this assignment including said application, any and all United States and foreign patents, utility models, and design registrations granted for any of said inventions or improvements, and the right to claim priority based on the filing date of said application under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and we authorize the Assignee to apply in all countries in our name or in its own name for patents, utility models, and design registrations and like rights of exclusion and for inventors' certificates for said inventions and improvements; and we agree for ourselves and our respective heirs, legal representatives and assigns, without further compensation to perform such lawful acts and to sign such further applications, assignments, Preliminary Statements and other lawful documents as the Assignee may reasonably request to effectuate fully this assignment.

Date: 7/3/95

M. Bhima Sankaram
Mantripragada Bhima Sankaram

Date: July 3, 1995

Sinil Kim MD
Sinil Kim

Substitute Form PTO-1595

08-03-1999

101106304

Attorney Docket No: 07833/001001

:R SHEET

f an original document

RECEIVED
AUG - 2

Assistant Commissioner for Pat

1. Name of conveying party(ies):

DepoTech Corporation

Additional name(s) attached? ☐ Yes ■ No

2. Name and address of receiving party(ies):

SkyePharma Inc.
10450 Science Center Drive
San Diego, CA 92121

Additional names/addresses attached? ☐ Yes ■ No

3. Nature of conveyance: 8-3-99
   - ☐ Assignment
   - ■ Merger
   - ☐ Security Agreement
   - ☐ Change of Name
   - ☐ Other:

Execution Date: **November 1, 1998**

4. Application number(s) or patent number(s):

If this document is being filed with a new application, the execution date of the application is:

A. Patent Application No.(s):

See Schedule A Attached

B. Patent No.(s):

See Schedule B Attached

Additional numbers attached? ■ Yes ☐ No

5. Name/address of party to whom correspondence concerning document should be mailed:

Diane L. Gardner
Fish & Richardson P.C.
4225 Executive Square, Suite 1400
La Jolla, CA 92037

6. Total number of applications/patents involved: **22**

7. Total fee (37 CFR 3.41): **$880**

   ■ Enclosed
   ☐ Authorized to charge deposit account

8. Deposit account number: **06-1050**

   If the fee above is being charged to deposit account, a duplicate copy of this cover sheet is attached. Please apply any additional charges, or any credits, to our Deposit Account No. 06-1050.

DO NOT USE THIS SPACE

9. Statement and signature: *To the best of my knowledge and belief, the foregoing information is true and correct and the attached is a true copy of the original document.*

Diane L. Gardner, Reg. No. 36,518 — Name of Person Signing

Signature

7/28/99 — Date

Total number of pages including cover sheet, attachments, and document: 7

880E

97966.LJ1

08/03/1999 MTHAI1 00000065 07563365

01 FC:581 880.00 DP

Schedule A
United States Pending Patent Applications

07/563,365	08/931,867
08/305,158	08/974,296
08/502,569	09/019,337
08/723,583	09/045,236
08/925,531	09/156,214
08/925,532	09/192,064

Schedule B
United States Issued Patents

5,173,219	5,723,147
5,422,120	5,759,573
5,455,044	5,766,627
5,576,017	5,807,572
5,576,018	5,891,467

97982.LJ1

AGREEMENT AND PLAN OF MERGER

between

SKYEPHARMA PLC

and

DEPOTECH CORPORATION

Dated as of November 1, 1998

AGREEMENT AND PLAN OF MERGER

AGREEMENT AND PLAN OF MERGER (hereinafter called this "Agreement"), dated as of November 1, 1998, between DepoTech Corporation, a California corporation (the "Company") and SkyePharma plc, a public limited company incorporated under the laws of England ("Parent").

RECITALS

WHEREAS, Parent intends to incorporate a corporation in California which will be a wholly-owned subsidiary of Parent ("Merger Sub," the Company and Merger Sub sometimes being hereinafter collectively referred to as the "Constituent Corporations") and which will be the vehicle through which the merger contemplated by this Agreement will be effected;

WHEREAS, Parent and Company intend to make the Merger Sub a party to this Agreement upon the official confirmation of incorporation of Merger Sub;

WHEREAS, the respective boards of directors of each of Parent and the Company have approved the merger of Merger Sub at the Effective Time (as defined herein) with and into the Company (the "Merger") and approved the Merger upon the terms and subject to the conditions set forth in this Agreement;

WHEREAS, it is intended that, for federal income tax purposes, the Merger shall qualify as a reorganization under the provisions of Section 368(a) of the Internal Revenue Code of 1986, as amended, and the rules and regulations promulgated thereunder (the "Code");

WHEREAS, the Company and Parent desire to, and Parent desires to cause Merger Sub to, make certain representations, warranties, covenants and agreements in connection with this Agreement; and

NOW, THEREFORE, in consideration of the premises, and of the representations, warranties, covenants and agreements contained herein, the parties hereto agree as follows:

ARTICLE I

The Merger; Closing; Effective Time

1.1 The Merger. Upon the terms and subject to the conditions set forth in this Agreement, at the Effective Time (as defined in Section 1.3) Merger Sub shall be merged with and into the Company and the separate corporate existence of Merger Sub shall thereupon cease. The Company shall be the surviving corporation in the Merger (sometimes hereinafter referred to as the "Surviving Corporation"), and the separate corporate existence of the Company with all its rights, privileges, immunities, powers and franchises shall continue unaffected by the Merger, except as set forth in Article II. The Merger shall have the effects specified in Section 1100, et seq, of the California Corporations Code (the "CCC").

1.2 Closing. The closing of the Merger (the "Closing") shall take place (i) at the offices of Brobeck, Phleger & Harrison LLP, 550 West C Street, Suite 1300 San Diego, California 92101 at 9:00 A.M. on the second business day after the day on which the last to be fulfilled or waived of the conditions set forth in Article VII (other than those conditions that by their nature are to be satisfied at the Closing, but subject to the fulfillment or waiver of those conditions) shall be satisfied or waived in accordance with this Agreement or (ii) at such other place and time and/or on such other date as the Company and Parent may agree in writing (the "Closing Date").

1.3 Effective Time. As soon as practicable following the Closing, the Company and Parent will cause a Plan of Merger with an officers' certificate of each of the Company and Merger Sub to be executed and filed with the Secretary of State of California in accordance with Section 1103 of the CCC, and the Merger shall thereupon become effective at the time of such filing (the "Effective Time").

ARTICLE II

Articles of Incorporation and By-Laws of the Surviving Corporation

2.1 The Articles of Incorporation. The articles of incorporation of the Company as in effect immediately prior to the Effective Time shall be the articles of incorporation of the Surviving Corporation (the "Charter"), until duly amended as provided therein or by applicable law, except that Article III of the Charter shall be amended to read in its entirety as follows: "The corporation is authorized to issue only one class of shares without par value; and the total number of shares which this corporation is authorized to issue is 1,000."

IN WITNESS WHEREOF, this Agreement has been duly executed and delivered by the duly authorized officers of the parties hereto as of the date first written above.

SKYEPHARMA PLC

By: _____
Name: P. BARBURTON
Title: COMPANY SECRETARY

DEPOTECH CORPORATION

By: _____
Name:
Title:

IN WITNESS WHEREOF, this Agreement has been duly executed and delivered by the duly authorized officers of the parties hereto as of the date first written above.

SKYEPHARMA PLC

By: _____
Name:
Title:

DEPOTECH CORPORATION

By: _____
Name: JOHN P LONGENECKER
Title: President & COO

Client Code: PCIRA.000GEN

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Director, U.S. Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party: (List using letters or numbers for multiple parties)

SkyePharma, Inc.

Additional name(s) of conveying party attached?

( ) Yes (X) No

2. Name and address of receiving party:

Name: Pacira Pharmaceuticals, Inc.
Street Address: 10450 Science Center Drive
City: San Diego **State:** CA
ZIP: 92121

Additional name(s) of receiving party attached?

( ) Yes (X) No

3. Nature of conveyance:

( ) Assignment ( ) Security Agreement
( ) Merger (X) Change of Name
( ) Other:

Execution Date: (List as in section 1 if multiple signatures)

May 31, 2007

4. US or PCT Application number(s) or US Patent number(s):

(X) Patent Application No.: 11/097,756
Filing Date: April 4, 2005

Additional numbers attached?

(X) Yes ( ) No

5. Party to whom correspondence concerning document should be mailed:

Customer No. 20,995
Address: Knobbe, Martens, Olson & Bear, LLP
2040 Main Street, 14th Floor
Irvine, CA 92614
Return Fax: (949) 760-9502
Attorney's Docket No.: PCIRA.000GEN

6. Total number of applications and patents involved:

28

7. Total fee (37 CFR 1.21(h)): $1,080

( ) Enclosed
(X) Authorized to be charged to deposit account if any additional fees are required, or to credit any overpayment

8. Deposit account number: 11-1410

Please charge this account for any additional fees which may be required, or credit any overpayment to this account.

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct, and any attached copy is a true copy of the original document.

Ian Jaquette
Name of Person Signing

60,866
Registration No.

Signature

2/22/08
Date

Total number of pages including cover sheet, attachments and document: 6

Documents transmitted via Facsimile to be recorded with required cover sheet information to:

Mail Stop Assignment Recordation Services
Director, U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
Facsimile Number: (571) 273-0140

4861406-skr-020808

700361393

RECORDATION FORM COVER SHEET
PATENTS ONLY (CONTINUED)

4. Application numbers or Patent numbers:

APPLICATIONS:

(X) Patent Application No.: 10/846,083
Filing Date: May 14, 2004

(X) Patent Application No.: 10/161,969
Filing Date: May 31, 2002

(X) Patent Application No.: 11/678,615
Filing Date: February 25, 2007

(X) Patent Application No.: 60/910,658
Filing Date: April 7, 2007

PATENTS:

(X) Patent No.: 5,766,627
Issue Date: June 16, 1998

(X) Patent No.: 5,455,044
Issue Date: October 3, 1995

(X) Patent No.: 5,576,018
Issue Date: November 19, 1996

(X) Patent No.: 5,993,850
Issue Date: November 30, 1999

(X) Patent No.: 5,931,809
Issue Date: August 3, 1999

(X) Patent No.: 6,428,529
Issue Date: August 6, 2002

(X) Patent No.: 6,045,824
Issue Date: April 4, 2000

(X) Patent No.: 6,106,858
Issue Date: August 22, 2000

RECORDATION FORM COVER SHEET
PATENTS ONLY (CONTINUED)

(X) Patent No.: 5,997,899
Issue Date: December 7, 1999

(X) Patent No.: 6,241,999
Issue Date: June 5, 2001

(X) Patent No.: 6,193,998
Issue Date: February 27, 2001

(X) Patent No.: 6,171,613
Issue Date: January 9, 2001

(X) Patent No.: 6,277,413
Issue Date: August 21, 2001

(X) Patent No.: 6,793,938
Issue Date: September 21, 2004

(X) Patent No.: 5,891,467
Issue Date: April 6, 1999

(X) Patent No.: 5,962,016
Issue Date: Ocotber 5, 1999

(X) Patent No.: 6,132,766
Issue Date: October 17, 2000

(X) Patent No.: 5,173,219
Issue Date: December 22, 1992

(X) Patent No.: 5,723,147
Issue Date: March 3, 1998

(X) Patent No.: 5,807,572
Issue Date: September 15, 1998

(X) Patent No.: 6,071,534
Issue Date: June 6, 2000

(X) Patent No.: 5,422,120
Issue Date: June 6, 1995

(X) Patent No.: 5,576,017
Issue Date: November 19, 1996

4861648-akr-020808

PACIRA
pharmaceuticals

Re: Pacira Pharmaceuticals, Inc. (formerly SkyePharma Inc.)
EIN: 33-0387911

To whom it may concern:

Effective June 1, 2007, SkyePharma Inc. completed a name change to Pacira Pharmaceuticals, Inc. This is solely a change in the name of the corporation and does not reflect any other changes in our business.

Attached is a copy of the amendment to the Company's existing Articles of Incorporation and the acknowledgement of the change from the State of California, which is the Company's state of incorporation.

If you have any questions regarding this matter, please contact the Company's Secretary, Thomas Zech at 858-625-2424 x3200 or by e-mail at: ThomasZ@pacira.com

A0662219

State of California
Secretary of State

I, DEBRA BOWEN, Secretary of State of the State of California, hereby certify:

That the attached transcript of 1 page(s) has been compared with the record on file in this office, of which it purports to be a copy, and that it is full, true and correct.

IN WITNESS WHEREOF, I execute this certificate and affix the Great Seal of the State of California this day of

JUN 14 2007

Debra Bowen

DEBRA BOWEN
Secretary of State

A0662219

ENDORSED - FILED
In the office of the Secretary of State
of the State of California
JUN - 1 2007

CERTIFICATE OF AMENDMENT OF
ARTICLES OF INCORPORATION
OF
SKYEPHARMA INC.

The undersigned hereby certify that:

1. They are the chairman of the board and the secretary, respectively, of SkyePharma Inc., a California corporation (the "Corporation").

2. Article I of the Articles of Incorporation of this Corporation is hereby amended and restated to read in its entirety as follows:

"The name of this corporation is Pacira Pharmaceuticals, Inc."

3. The amendment to the Articles of Incorporation as set forth herein has been duly approved by the Board of Directors of this Corporation pursuant to Sections 902 of the California Corporations Code.

4. The amendment to the Articles of Incorporation of this corporation as set forth herein has been duly approved by the required vote of shareholders in accordance with Sections 902 of the California Corporations Code. The total number of outstanding shares of the corporation is One Thousand (1,000) shares of common stock. The number of shares voting in favor of the amendment equaled or exceeded the vote required. The percentage vote required was more than 50%.

The undersigned, Fred A. Middleton and Thomas Zech, the Chairman of the Board and Secretary, respectively, of SkyePharma Inc. declare under penalty of perjury under the laws of the State of California that the matters set forth in this certificate are true and correct of their own knowledge.

Date: May 31, 2007

Fred A. Middleton
Chairman of the Board

Thomas M. Zech
Secretary

OFFICE OF THE SECRETARY OF STATE

EXHIBIT B

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EXPAREL™ safely and effectively. See full prescribing information for EXPAREL.

EXPAREL (Bupivacaine Liposome Injectable Suspension)
Initial U.S. Approval: 1972

INDICATIONS AND USAGE

EXPAREL is a liposome injection of bupivacaine, an amide local anesthetic, indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia (1).

DOSAGE AND ADMINISTRATION

EXPAREL is intended for single-dose administration only. The recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area.

Surgery	Dose of EXPAREL	Volume of EXPAREL
Bunionectomy	106 mg	8 mL
Hemorrhoidectomy	266 mg	20 mL

Inject EXPAREL slowly into soft tissue via infiltration (2.1).

DOSAGE FORMS AND STRENGTHS

EXPAREL (bupivacaine liposome injectable suspension)
10 mL single use vial, 1.3% (13.3 mg/mL) (3)
20 mL single use vial, 1.3% (13.3 mg/mL) (3)

CONTRAINDICATIONS

EXPAREL is contraindicated in obstetrical paracervical block anesthesia (4).

WARNINGS AND PRECAUTIONS

- Monitoring of cardiovascular and neurological status, as well as vital signs should be performed during and after injection of EXPAREL as with other local anesthetic products (5.1).
- Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations (5.1).
- Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL (5.2).

ADVERSE REACTIONS

Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration were nausea, constipation, and vomiting (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Pacira Pharmaceuticals, Inc. at 858-625-2414 ext. 3231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- EXPAREL should not be admixed with lidocaine or other non-bupivacaine-based local anesthetics (7).
- EXPAREL may be administered after at least 20 minutes or more have elapsed following local administration of lidocaine.

USE IN SPECIAL POPULATIONS

Safety and effectiveness in pediatric patients below the age of 18 have not been established (8).

See 17 for PATIENT COUNSELING INFORMATION

Revised: October 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

EXPAREL is a liposome injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia.

EXPAREL has not been studied for use in patients younger than 18 years of age.

2. DOSAGE AND ADMINISTRATION

EXPAREL is intended for single-dose administration only. The recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area.

Surgery	Dose of EXPAREL	Volume of EXPAREL
Bunionectomy[1]	106 mg	8 mL
Hemorrhoidectomy[2]	266 mg	20 mL

[1]Infiltrate 7 mL of EXPAREL into the tissues surrounding the osteotomy and 1 mL into the subcutaneous tissue.

[2]Dilute 20 mL of EXPAREL with 10 mL of saline, for a total of 30 mL, and divide the mixture into six 5 mL aliquots. Perform the anal block by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers.

2.1 Injection Instructions

EXPAREL should be injected slowly into soft tissues of the surgical site with frequent aspiration to check for blood and minimize the risk of intravascular injection.

- EXPAREL is intended for single-dose infiltration only.
- EXPAREL should be administered with a 25 gauge or larger bore needle.
- The maximum dosage of EXPAREL should not exceed 266 mg (20 mL, 1.3% of undiluted drug).
- Do not administer EXPAREL if the product is discolored.
- Do not administer EXPAREL if it is suspected that the vial has been frozen as reflected by the temperature indicator or exposed to high temperature (greater than 40°C or 104°F) for an extended period.
- EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e. 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection.
- Vials of EXPAREL should be inverted multiple times to re-suspend the particles immediately prior to withdrawal from the vial.

- Diluted suspensions of EXPAREL should be used within 4 hours of preparation in a syringe.

2.2 Administration Precautions

Some physicochemical incompatibilities exist between EXPAREL and certain other drugs. Direct contact of EXPAREL with these drugs results in a rapid increase in free (unencapsulated) bupivacaine, altering EXPAREL characteristics and potentially affecting the safety and efficacy of EXPAREL. Therefore, admixing EXPAREL with other drugs prior to administration is not recommended [*See Drug Interactions (7)*].

- Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl, when injected immediately before EXPAREL, may impact the pharmacokinetic and/or physicochemical properties of the drugs when the milligram dose of bupivacaine HCl solution exceeds 50% of the EXPAREL dose. EXPAREL contains bupivacaine; therefore, coadministration of both drugs will increase the overall exposure to bupivacaine.
- When a topical antiseptic such as povidone iodine (e.g., Betadine®) is applied, the site should be allowed to dry before EXPAREL is administered into the surgical site. EXPAREL should not be allowed to come into contact with antiseptics such as povidone iodine in solution.

Studies conducted with EXPAREL demonstrated that the most common implantable materials (polypropylene, PTFE, silicone, stainless steel, and titanium) are not affected by the presence of EXPAREL any more than they are by saline. None of the materials studied had an adverse effect on EXPAREL.

When administered in recommended doses and concentrations, bupivacaine HCl does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

2.3 Non-Interchangeability with Other Formulations of Bupivacaine

Different formulations of bupivacaine are not bioequivalent even if the milligram dosage is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL and vice versa.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

2.4 Dosing in Special Populations

EXPAREL has not been studied in patients younger than 18 years of age, pregnant patients or patients who are nursing.

3. DOSAGE FORMS AND STRENGTHS

EXPAREL (bupivacaine liposome injectable suspension)

- 10 mL single use vial, 1.3% (13.3 mg/mL)
- 20 mL single use vial, 1.3% (13.3 mg/mL)

4. CONTRAINDICATIONS

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. While EXPAREL has not been tested with this technique, the use of bupivacaine HCl with this technique has resulted in fetal bradycardia and death.

5. WARNINGS AND PRECAUTIONS

5.1 Warnings and Precautions for Bupivacaine containing Products

The safety and effectiveness of bupivacaine and other amide-containing products depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine, any bupivacaine-containing product should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity [*See Overdosage (10)*].

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after injection of bupivacaine and other amide-containing products. Restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Bupivacaine and other amide-containing products should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs.

Injection of multiple doses of bupivacaine and other amide-containing products may cause significant increases in plasma concentrations with each repeated dose due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood concentrations varies with the status of the patient.

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

Central Nervous System Reactions

The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon

the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug. Neurologic effects following infiltration of soft tissue may include persistent anesthesia, paresthesias, weakness, and paralysis, all of which may have slow, incomplete, or no recovery.

Central nervous system reactions are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils. The incidence of convulsions associated with the use of local anesthetics varies with the procedure used and the total dose administered.

Cardiovascular System Reactions

Toxic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure [*See Warnings and Precautions (5.1) and Overdosage (10)*].

Allergic Reactions

Allergic-type reactions are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Chondrolysis

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been postmarketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humerol chondrolysis have been described in pediatric patients and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness, and loss of motion can be variable, but may begin as early as the second month after surgery. Currently, there is no effective treatment for chondrolysis; patients who have experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

5.2 Warnings and Precautions Specific for EXPAREL

As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine, EXPAREL should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity [*See Overdosage (10)*].

Caution should be taken to avoid accidental intravascular injection of EXPAREL. Convulsions and cardiac arrest have occurred following accidental intravascular injection of bupivacaine and other amide-containing products.

Using EXPAREL followed by other bupivacaine formulations has not been studied in clinical trials. Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL [*See Clinical Pharmacology (12.3)*].

EXPAREL has not been evaluated for the following uses and, therefore, is not recommended for these types of analgesia or routes of administration.

- epidural
- intrathecal
- regional nerve blocks
- intravascular or intra-articular use

EXPAREL has not been evaluated for use in the following patient population and, therefore, it is not recommended for administration to these groups.

- patients younger than 18 years old
- pregnant patients
- nursing patients

The ability of EXPAREL to achieve effective anesthesia has not been studied. Therefore, EXPAREL is not indicated for pre-incisional or pre-procedural loco-regional anesthetic techniques that require deep and complete sensory block in the area of administration.

6. ADVERSE REACTIONS

6.1 General

The most commonly encountered acute adverse experiences to bupivacaine and all amide-type local anesthetics that demand immediate counter-measures are related to the central nervous and cardiovascular systems.

High plasma concentrations of bupivacaine can occur from overdosage, unintended intravascular injection, or accumulation of bupivacaine in plasma secondary to decreased hepatic metabolic degradation of the drug or diminished plasma protein binding capacity due to acidosis, pathologically lowered plasma protein production, or competition with other drugs for protein binding sites. Although rare, some individuals have a lower tolerance to and are supersensitive

to bupivacaine and other amide-type local anesthetics and may rapidly develop signs of toxicity at low doses [*See Overdosage (10)*].

6.2 Adverse Reactions Reported in All Wound Infiltration Clinical Studies

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety of EXPAREL was evaluated in 10 randomized, double-blind, local administration into the surgical site clinical studies involving 823 patients undergoing various surgical procedures. Patients were administered a dose ranging from 66 to 532 mg of EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, constipation, and vomiting.

The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration were pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.

The less common/rare adverse reactions (incidence less than 2%) following EXPAREL administration were chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, dizziness postural, paresthesia, syncope, incision site edema, procedural hypertension, procedural hypotension, procedural nausea, muscular weakness, neck pain, pruritus generalized, rash pruritic, hyperhidrosis, cold sweat, urticaria, bradycardia, palpitations, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, ventricular tachycardia, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory depression, respiratory failure, body temperature increased, blood pressure increased, blood pressure decreased, oxygen saturation decreased, urinary retention, urinary incontinence, vision blurred, tinnitus, drug hypersensitivity, and hypersensitivity.

Neurological and Cardiac Adverse Reactions Reported in All Wound Infiltration Clinical Studies

In the EXPAREL wound infiltration studies, adverse reactions with an incidence greater than or equal to 1% in the Nervous System Disorders system organ class following EXPAREL administration were dizziness (6.2%), headache (3.8%), somnolence (2.1%), hypoesthesia (1.5%), and lethargy (1.3%). The adverse reactions with an incidence greater than or equal to 1% in the Cardiac Disorders system organ class following EXPAREL administration were tachycardia (3.9%) and bradycardia (1.6%).

Adverse Reactions Reported in Placebo-Controlled Wound Infiltration Clinical Studies

Adverse reactions with an incidence greater than or equal to 2% reported by patients in clinical studies comparing 8 mL EXPAREL 1.3% (106 mg) to placebo and 20 mL EXPAREL 1.3% (266 mg) to placebo are shown in Table 1.

Table 1: Treatment-Emergent Adverse Reactions (TEAE) with an Incidence Greater than or Equal to 2%: Placebo-Controlled Studies

	STUDY 1[a]		STUDY 2[b]	
	EXPAREL 8 mL/1.3% (106 mg)	Placebo	EXPAREL 20 mL/1.3% (266 mg)	Placebo
System Organ Class Preferred Term	(N=97) n (%)	(N=96) n (%)	(N=95) n (%)	(N=94) n (%)
Any TEAE	53 (54.6)	59 (61.5)	10 (10.5)	17 (18.1)
Gastrointestinal Disorders	41 (42.3)	38 (39.6)	7 (7.4)	13 (13.8)
Nausea	39 (40.2)	36 (37.5)	2 (2.1)	1 (1.1)
Vomiting	27 (27.8)	17 (17.7)	2 (2.1)	4 (4.3)
Constipation	2 (2.1)	1 (1.0)	2 (2.1)	2 (2.1)
Anal Hemorrhage	0 (0.0)	0 (0.0)	3 (3.2)	4 (4.3)
Painful Defecation	0 (0.0)	0 (0.0)	2 (2.1)	5 (5.3)
Rectal Discharge	0 (0.0)	0 (0.0)	1 (1.1)	3 (3.2)
Nervous System Disorders	20 (20.6)	30 (31.3)	0 (0.0)	0 (0.0)
Dizziness	11 (11.3)	25 (26.0)	0 (0.0)	0 (0.0)
Headache	5 (5.2)	8 (8.3)	0 (0.0)	0 (0.0)
Somnolence	5 (5.2)	1 (1.0)	0 (0.0)	0 (0.0)
Syncope	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin And Subcutaneous Tissue Disorders	8 (8.2)	7 (7.3)	0 (0.0)	0 (0.0)
Pruritus Generalized	5 (5.2)	6 (6.3)	0 (0.0)	0 (0.0)
Pruritus	3 (3.1)	1 (1.0)	0 (0.0)	0 (0.0)
Investigations	5 (5.2)	3 (3.1)	4 (4.2)	3 (3.2)
Alanine Aminotransferase Increased	3 (3.1)	3 (3.1)	1 (1.1)	0 (0.0)
Aspartate Aminotransferase Increased	3 (3.1)	2 (2.1)	0 (0.0)	0 (0.0)
Blood Creatinine Increased	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Body Temperature Increased	0 (0.0)	0 (0.0)	3 (3.2)	3 (3.2)

System Organ Class Preferred Term	STUDY 1[a] EXPAREL 8 mL/1.3% (106 mg) (N=97) n (%)	 Placebo (N=96) n (%)	STUDY 2[b] EXPAREL 20 mL/1.3% (266 mg) (N=95) n (%)	 Placebo (N=94) n (%)
General Disorders And Administration Site Conditions	4 (4.1)	0 (0.0)	1 (1.1)	1 (1.1)
Feeling Hot	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	2 (2.1)	0 (0.0)	1 (1.1)	1 (1.1)
Infections And Infestations	2 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)
Fungal Infection	2 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)
Injury, Poisoning And Procedural Complications	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Post Procedural Swelling	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism And Nutrition Disorders	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)
Decreased Appetite	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)

[a] Study 1: Bunionectomy
[b] Study 2: Hemorrhoidectomy
At each level of summation (overall, system organ class, preferred term), patients are only counted once.
Preferred terms are included where at least 2% of patients reported the event in any treatment group.
TEAE = treatment-emergent adverse event.

7. DRUG INTERACTIONS

EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e., 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection. EXPAREL must not be diluted with water or other hypotonic agents as it will result in disruption of the liposomal particles.

EXPAREL should not be admixed with lidocaine or other non-bupivacaine-based local anesthetics.

EXPAREL may be locally administered after at least 20 minutes following local administration of lidocaine.

EXPAREL should not be admixed with other drugs prior to administration.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women of the effect of bupivacaine on the developing fetus. EXPAREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Bupivacaine hydrochloride (HCl) produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. This does not exclude the use of EXPAREL at term for analgesia [*See Labor and Delivery (8.2)*].

Bupivacaine HCl was administered subcutaneously to rats and rabbits during the period of fetal organogenesis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity.

Administration of bupivacaine HCl to rats during pregnancy and lactation resulted in decreased offspring survival.

8.2 Labor and Delivery

Bupivacaine hydrochloride is contraindicated for obstetrical paracervical block anesthesia.

Local anesthetics rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity [*See Clinical Pharmacology (12.3)*]. The incidence and degree of toxicity depend upon the procedure performed, the type, and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

8.3 Nursing mothers

Bupivacaine has been reported to be excreted to some extent in human milk, suggesting that the nursing infant could be theoretically exposed to a dose of the drug. Because of the potential for serious adverse reactions in nursing infants from bupivacaine, a decision should be made whether to discontinue nursing or not administer EXPAREL, taking into account the importance of the drug to the mother.

8.4 Pediatric use

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

8.5 Geriatric use

Of the total number of patients in the EXPAREL wound infiltration clinical studies (N=823), 171 patients were greater than or equal to 65 years of age and 47 patients were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients. Clinical experience with EXPAREL has not identified differences in efficacy or safety between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients. Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to bupivacaine may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection of EXPAREL.

8.6 Hepatic Impairment

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

8.7 Renal Impairment

Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Care should be taken in dose selection of EXPAREL.

10. OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma concentrations encountered during therapeutic use of local anesthetics or to unintended intravascular injection of local anesthetic solution [*See Warnings and Precautions (5) and Adverse Reactions (6)*].

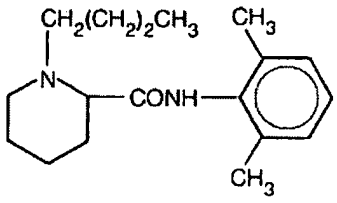
In the clinical study program, maximum plasma concentration (C_{max}) values of approximately 34,000 ng/mL were reported and likely reflected inadvertent intravascular administration of EXPAREL or systemic absorption of EXPAREL at the surgical site. The plasma bupivacaine measurements did not discern between free and liposomal-bound bupivacaine making the clinical relevance of the reported values uncertain; however, no discernable adverse events or clinical sequelae were observed in these patients.

11. DESCRIPTION

EXPAREL is a sterile, non-pyrogenic white to off-white preservative-free aqueous suspension of multivesicular liposomes (DepoFoam® drug delivery system) containing bupivacaine. Bupivacaine is present at a concentration of 13.3 mg/mL. After injection of EXPAREL into soft tissue, bupivacaine is released from the multivesicular liposomes over a period of time.

11.1 Active Ingredient

Bupivacaine is related chemically and pharmacologically to the amide-type local anesthetics. It is a homologue of mepivacaine and is related chemically to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino, or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage. Chemically, bupivacaine is 1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide with a molecular weight of 288.4. Bupivacaine has the following structural formula:



Bupivacaine is present in EXPAREL at a concentration of 13.3 mg/mL.

11.2 Lipid Formulation

The median diameter of the liposome particles ranges from 24 to 31 μm. The liposomes are suspended in a 0.9% sodium chloride solution. Each vial contains bupivacaine at a nominal concentration of 13.3 mg/mL. Inactive ingredients and their nominal concentrations are: cholesterol, 4.7 mg/mL; 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), 0.9 mg/mL; tricaprylin, 2.0 mg/mL; and 1, 2-dierucoylphosphatidylcholine (DEPC), 8.2 mg/mL. The pH of EXPAREL is in the range of 5.8 to 7.4.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Local anesthetics block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.2 Pharmacodynamics

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems. At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after accidental intravascular injection of bupivacaine.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors, and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.

12.3 Pharmacokinetics

Local infiltration of EXPAREL results in significant systemic plasma levels of bupivacaine which can persist for 96 hours [*See Warnings and Precautions (5.2)*]. Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy.

Absorption

The rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site.

Pharmacokinetic parameters of EXPAREL after local administration were evaluated following surgical procedures. Descriptive statistics of pharmacokinetic parameters of representative EXPAREL doses in each study are provided in Table 2.

Table 2: Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of EXPAREL

	EXPAREL	
	Bunionectomy 106 mg (8 mL)	**Hemorrhoidectomy 266 mg (20 mL)**
	(N=26)	**(N=25)**
C_{max} (ng/mL)	166 (92.7)	867 (353)
T_{max} (h)	2	0.5
$AUC_{(0-t)}$ (h×ng/mL)	5864 (2038)	16,867 (7868)
$AUC_{(inf)}$ (h×ng/mL)	7105 (2283)	18,289 (7569)
$t_{½}$ (h)	34.1 (17.0)	23.8 (39.4)

Note: Arithmetic mean (standard deviation) except T_{max} (median).

Distribution

After bupivacaine has been released from EXPAREL and is absorbed systemically, bupivacaine distribution is expected to be the same as for any bupivacaine HCl solution formulation.

Local anesthetics including bupivacaine are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Local anesthetics including bupivacaine appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid

soluble, non-ionized drugs such as bupivacaine readily enter the fetal blood from the maternal circulation.

Metabolism

Amide-type local anesthetics, such as bupivacaine, are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecolylxylidine (PPX) is the major metabolite of bupivacaine; approximately 5% of bupivacaine is converted to PPX. Elimination of drug depends largely upon the availability of plasma protein binding sites in the circulation to carry it to the liver where it is metabolized.

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic disease. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics.

Excretion

After bupivacaine has been released from EXPAREL and is absorbed systemically, bupivacaine excretion is expected to be the same as for other bupivacaine formulations.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Only 6% of bupivacaine is excreted unchanged in the urine.

Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Acidifying the urine hastens the renal elimination of local anesthetics. Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of renal disease, factors affecting urinary pH, and renal blood flow.

Specific Populations

Hepatic Impairment

The effects of decreased hepatic function on bupivacaine pharmacokinetics following administration of EXPAREL were studied in patients with moderate hepatic impairment. Consistent with the hepatic clearance of bupivacaine, mean plasma concentrations were higher in patients with moderate hepatic impairment than in the healthy control volunteers with approximately 1.5- and 1.6-fold increases in the mean values for C_{max} and the area under the curve (AUC), respectively.

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations [*See Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].

Renal Impairment

Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Care should be taken in dose selection of EXPAREL [*See Use in Specific Populations (8.7)*].

Age

Various pharmacokinetic parameters of the local anesthetics such as bupivacaine can be significantly altered by the age of the patient.

In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients.

Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection of EXPAREL [*See Use in Specific Populations (8.5)*].

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies in animals of most local anesthetics, including bupivacaine, to evaluate the carcinogenic potential have not been conducted. Mutagenic potential and the effect on fertility have not been determined. There is no evidence from human data that bupivacaine may be carcinogenic or mutagenic or that it impairs fertility.

14. CLINICAL STUDIES

The efficacy of EXPAREL was compared to placebo in two multicenter, randomized, double-blinded clinical trials. One trial evaluated the treatments in patients undergoing bunionectomy; the other trial evaluated the treatments in patients undergoing hemorrhoidectomy. EXPAREL has not been demonstrated to be safe and effective in other procedures.

14.1 Bunionectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of 106 mg EXPAREL in 193 patients undergoing bunionectomy. The mean age was 43 years (range 18 to 72). Study medication was administered directly into the wound at the conclusion of the surgery, prior to wound closure. Pain intensity was rated by the patients on a 0 to 10 numeric rating scale (NRS) out to 72 hours. Postoperatively, patients were allowed rescue medication (5 mg oxycodone/325 mg acetaminophen orally every 4 to 6 hours as needed) or, if that was insufficient within the first 24 hours, ketorolac (15 to 30 mg IV). The primary outcome measure was the area under the curve (AUC) of the NRS pain intensity scores (cumulative pain scores) collected over the first 24 hour period. There was a significant treatment effect for EXPAREL compared to placebo.

In this clinical study, EXPAREL demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours. The difference in mean pain intensity between treatment groups occurred only during the first 24 hours following study drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between EXPAREL and placebo treatments on mean pain intensity.

14.2 Hemorrhoidectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of 266 mg EXPAREL in 189 patients undergoing hemorrhoidectomy. The mean age was 48 years (range 18 to 86). Study medication was administered directly into the wound (greater than or equal to 3 cm) at the conclusion of the surgery. Pain intensity was rated by the patients on a 0 to 10 NRS at multiple time points up to 72 hours. Postoperatively, patients were allowed rescue medication (morphine sulfate 10 mg intramuscular every 4 hours as needed). The primary outcome measure was the AUC of the NRS pain intensity scores (cumulative pain scores) collected over the first 72 hour period. There was a significant treatment effect for EXPAREL compared to placebo.

In this clinical study, EXPAREL demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours. The difference in mean pain intensity between treatment groups occurred only during the first 24 hours following study drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between EXPAREL and placebo treatments on mean pain intensity; however, there was an attendant decrease in opioid consumption, the clinical benefit of which was not demonstrated.

16. HOW SUPPLIED/STORAGE AND HANDLING

EXPAREL (bupivacaine liposome injectable suspension) is available in single-use vials for infiltration.

10 mL single use vial, 1.3% (13.3 mg/mL) packaged in cartons of 10 (NDC 65250-133-10)

20 mL single use vial, 1.3% (13.3 mg/mL) packaged in cartons of 10 (NDC 65250-266-20)

Different formulations of bupivacaine are not bioequivalent even if the milligram strength is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL.

Storage

EXPAREL vials should be stored refrigerated between 2°C to 8°C (36°F to 46°F). EXPAREL may be held at a controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to one month in sealed, intact (unopened) vials. Vials should not be re-refrigerated. As a convenience to the hospital pharmacist, each vial label includes space to record the date when the vial has been removed from refrigeration.

EXPAREL should not be frozen as reflected by the temperature indicator or exposed to high temperatures (greater than 40°C or 104°F) for an extended period. Do not administer EXPAREL if it is suspected of having been frozen as reflected by the temperature indicator or exposed to high temperatures.

Check the freeze indicator and discard product if it has been triggered. The freeze indicator turns from green to white when exposed to freezing temperatures.

Handling

- Vials of EXPAREL should be inverted to re-suspend the particles immediately prior to withdrawal from the vial. Multiple inversions may be necessary to re-suspend the particles if the contents of the vial have settled.
- Vials should be visually inspected before use.
- Do not filter.
- Do not heat before use.
- Do not autoclave.
- EXPAREL should be administered with a 25 gauge or larger bore needle.
- EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e. 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection.
- Following withdrawal from the vial, EXPAREL may be stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 4 hours prior to administration.
- Discard any unused portion in an appropriate manner.

17. PATIENT COUNSELING INFORMATION

Patients should be informed in advance that bupivacaine-containing products can cause temporary loss of sensation or motor activity in the area infiltrated. Physicians should discuss adverse reactions in the EXPAREL prescribing information with their patients.

Pacira Pharmaceuticals, Inc.

San Diego, CA 92121 USA

Patent Numbers:

6,132,766

5,766,627

5,891,467

Trademark of Pacira Pharmaceuticals, Inc.

PACIRA

PHARMACEUTICALS, INC

EXHIBIT C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022496

NDA APPROVAL

Pacira Pharmaceuticals, Inc.
10450 Science Center Dr.
San Diego, CA 92121

Attention: Dwain Allen
Director, Regulatory Affairs

Dear Mr. Allen:

Please refer to your New Drug Application (NDA) dated and received September 28, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for EXPAREL (bupivacaine liposome injectable suspension).

We acknowledge receipt of your amendments dated October 21, November 8, 12, 18, and 23, December 9 and 22, 2010, and January 28, February 1, 4, 9 (2), and 24, March 2, and 17, April 5, 7, 14, 18 and 27, May 5, 13, 20 and 25, June 14, July 1, 14, 15, 22, 25, 26, and 27 (2), August 26, September 2, 6, 12, 13, 20, 22, 26 (2) and 29, and October 17, 20, and 24, 2011.

This new drug application provides for the use of EXPAREL (bupivacaine liposome injectable suspension) for single-dose infiltration into the surgical site to produce postsurgical analgesia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022496.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for ages 0 to less than 17 years for this application because this product is ready for approval for use in adults and pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1834-1 Multicenter, randomized, double-blind, parallel-group, bupivacaine- and placebo-controlled study to evaluate the safety, efficacy and pharmacokinetic profile of a single intraoperative administration of Exparel for postoperative analgesia in adolescent subjects 12 to less than 17 years old undergoing multiple surgical procedures.

Final Protocol Submission:	October 2012
Study/Trial Completion:	November 2013
Final Report Submission:	February 2014

1834-2 A multicenter, randomized, double-blind, parallel-group, Bupivacaine- and placebo-controlled study to evaluate the safety, efficacy and pharmacokinetic

profile of a single intraoperative administration of Exparel for postoperative analgesia in children 6 to 11 years old undergoing multiple surgical procedures.

Final Protocol Submission: April 2014
Study/Trial Completion: May 2015
Final Report Submission: August 2015

1834-3 A multicenter, randomized, double-blind, parallel-group, bupivacaine- and placebo-controlled study to evaluate the safety, efficacy and pharmacokinetic profile of a single intraoperative administration of Exparel for postoperative analgesia in young children 2 to 5 years old undergoing multiple surgical procedures.

Final Protocol Submission: October 2015
Study/Trial Completion: November 2016
Final Report Submission: February 2017

1834-4 A multicenter, randomized, double-blind, parallel-group, bupivacaine- and placebo-controlled study to evaluate the safety, efficacy and pharmacokinetic profile of a single intraoperative administration of Exparel for postoperative analgesia in young children 0 to 1 years old undergoing multiple surgical procedures.

Final Protocol Submission: August 2017
Study/Trial Completion: February 2019
Final Report Submission: May 2019

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

EXPIRATION DATING PERIOD

A 24-month expiration dating period is granted for the drug product, when stored at 2° C to 8°C (36°F to 46°F).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sharon Turner-Rinehardt, Senior Regulatory Health Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EXPAREL™ safely and effectively. See full prescribing information for EXPAREL.

EXPAREL (Bupivacaine Liposome Injectable Suspension)
Initial U.S. Approval: 1972

INDICATIONS AND USAGE

EXPAREL is a liposome injection of bupivacaine, an amide local anesthetic, indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia (1).

DOSAGE AND ADMINISTRATION

EXPAREL is intended for single-dose administration only. The recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area.

Surgery	Dose of EXPAREL	Volume of EXPAREL
Bunionectomy	106 mg	8 mL
Hemorrhoidectomy	266 mg	20 mL

Inject EXPAREL slowly into soft tissue via infiltration (2.1).

DOSAGE FORMS AND STRENGTHS

EXPAREL (bupivacaine liposome injectable suspension)
10 mL single use vial, 1.3% (13.3 mg/mL) (3)
20 mL single use vial, 1.3% (13.3 mg/mL) (3)

CONTRAINDICATIONS

EXPAREL is contraindicated in obstetrical paracervical block anesthesia (4).

WARNINGS AND PRECAUTIONS

- Monitoring of cardiovascular and neurological status, as well as vital signs should be performed during and after injection of EXPAREL as with other local anesthetic products (5.1).
- Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations (5.1).
- Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL (5.2).

ADVERSE REACTIONS

Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration were nausea, constipation, and vomiting (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Pacira Pharmaceuticals, Inc. at 858-625-2414 ext. 3231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- EXPAREL should not be admixed with lidocaine or other non-bupivacaine-based local anesthetics (7).
- EXPAREL may be administered after at least 20 minutes or more have elapsed following local administration of lidocaine.

USE IN SPECIAL POPULATIONS

Safety and effectiveness in pediatric patients below the age of 18 have not been established (8).

See 17 for PATIENT COUNSELING INFORMATION

Revised: October 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

EXPAREL is a liposome injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia.

EXPAREL has not been studied for use in patients younger than 18 years of age.

2. DOSAGE AND ADMINISTRATION

EXPAREL is intended for single-dose administration only. The recommended dose of EXPAREL is based on the surgical site and the volume required to cover the area.

Surgery	Dose of EXPAREL	Volume of EXPAREL
Bunionectomy[1]	106 mg	8 mL
Hemorrhoidectomy[2]	266 mg	20 mL

[1]Infiltrate 7 mL of EXPAREL into the tissues surrounding the osteotomy and 1 mL into the subcutaneous tissue.

[2]Dilute 20 mL of EXPAREL with 10 mL of saline, for a total of 30 mL, and divide the mixture into six 5 mL aliquots. Perform the anal block by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers.

2.1 Injection Instructions

EXPAREL should be injected slowly into soft tissues of the surgical site with frequent aspiration to check for blood and minimize the risk of intravascular injection.

- EXPAREL is intended for single-dose infiltration only.
- EXPAREL should be administered with a 25 gauge or larger bore needle.
- The maximum dosage of EXPAREL should not exceed 266 mg (20 mL, 1.3% of undiluted drug).
- Do not administer EXPAREL if the product is discolored.
- Do not administer EXPAREL if it is suspected that the vial has been frozen as reflected by the temperature indicator or exposed to high temperature (greater than 40°C or 104°F) for an extended period.
- EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e. 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection.
- Vials of EXPAREL should be inverted multiple times to re-suspend the particles immediately prior to withdrawal from the vial.

- Diluted suspensions of EXPAREL should be used within 4 hours of preparation in a syringe.

2.2 Administration Precautions

Some physicochemical incompatibilities exist between EXPAREL and certain other drugs. Direct contact of EXPAREL with these drugs results in a rapid increase in free (unencapsulated) bupivacaine, altering EXPAREL characteristics and potentially affecting the safety and efficacy of EXPAREL. Therefore, admixing EXPAREL with other drugs prior to administration is not recommended [*See Drug Interactions (7)*].

- Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl, when injected immediately before EXPAREL, may impact the pharmacokinetic and/or physicochemical properties of the drugs when the milligram dose of bupivacaine HCl solution exceeds 50% of the EXPAREL dose. EXPAREL contains bupivacaine; therefore, coadministration of both drugs will increase the overall exposure to bupivacaine.
- When a topical antiseptic such as povidone iodine (e.g., Betadine®) is applied, the site should be allowed to dry before EXPAREL is administered into the surgical site. EXPAREL should not be allowed to come into contact with antiseptics such as povidone iodine in solution.

Studies conducted with EXPAREL demonstrated that the most common implantable materials (polypropylene, PTFE, silicone, stainless steel, and titanium) are not affected by the presence of EXPAREL any more than they are by saline. None of the materials studied had an adverse effect on EXPAREL.

When administered in recommended doses and concentrations, bupivacaine HCl does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

2.3 Non-Interchangeability with Other Formulations of Bupivacaine

Different formulations of bupivacaine are not bioequivalent even if the milligram dosage is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL and vice versa.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

2.4 Dosing in Special Populations

EXPAREL has not been studied in patients younger than 18 years of age, pregnant patients or patients who are nursing.

3. DOSAGE FORMS AND STRENGTHS

EXPAREL (bupivacaine liposome injectable suspension)

- 10 mL single use vial, 1.3% (13.3 mg/mL)
- 20 mL single use vial, 1.3% (13.3 mg/mL)

4. CONTRAINDICATIONS

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. While EXPAREL has not been tested with this technique, the use of bupivacaine HCl with this technique has resulted in fetal bradycardia and death.

5. WARNINGS AND PRECAUTIONS

5.1 Warnings and Precautions for Bupivacaine containing Products

The safety and effectiveness of bupivacaine and other amide-containing products depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine, any bupivacaine-containing product should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity [*See Overdosage (10)*].

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after injection of bupivacaine and other amide-containing products. Restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Bupivacaine and other amide-containing products should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs.

Injection of multiple doses of bupivacaine and other amide-containing products may cause significant increases in plasma concentrations with each repeated dose due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood concentrations varies with the status of the patient.

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

Central Nervous System Reactions

The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon

the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug. Neurologic effects following infiltration of soft tissue may include persistent anesthesia, paresthesias, weakness, and paralysis, all of which may have slow, incomplete, or no recovery.

Central nervous system reactions are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils. The incidence of convulsions associated with the use of local anesthetics varies with the procedure used and the total dose administered.

Cardiovascular System Reactions

Toxic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure [*See Warnings and Precautions (5.1) and Overdosage (10)*].

Allergic Reactions

Allergic-type reactions are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Chondrolysis

Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been postmarketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humerol chondrolysis have been described in pediatric patients and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness, and loss of motion can be variable, but may begin as early as the second month after surgery. Currently, there is no effective treatment for chondrolysis; patients who have experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement.

5.2 Warnings and Precautions Specific for EXPAREL

As there is a potential risk of severe life-threatening adverse effects associated with the administration of bupivacaine, EXPAREL should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity [*See Overdosage (10)*].

Caution should be taken to avoid accidental intravascular injection of EXPAREL. Convulsions and cardiac arrest have occurred following accidental intravascular injection of bupivacaine and other amide-containing products.

Using EXPAREL followed by other bupivacaine formulations has not been studied in clinical trials. Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL [*See Clinical Pharmacology (12.3)*].

EXPAREL has not been evaluated for the following uses and, therefore, is not recommended for these types of analgesia or routes of administration.

- epidural
- intrathecal
- regional nerve blocks
- intravascular or intra-articular use

EXPAREL has not been evaluated for use in the following patient population and, therefore, it is not recommended for administration to these groups.

- patients younger than 18 years old
- pregnant patients
- nursing patients

The ability of EXPAREL to achieve effective anesthesia has not been studied. Therefore, EXPAREL is not indicated for pre-incisional or pre-procedural loco-regional anesthetic techniques that require deep and complete sensory block in the area of administration.

6. ADVERSE REACTIONS

6.1 General

The most commonly encountered acute adverse experiences to bupivacaine and all amide-type local anesthetics that demand immediate counter-measures are related to the central nervous and cardiovascular systems.

High plasma concentrations of bupivacaine can occur from overdosage, unintended intravascular injection, or accumulation of bupivacaine in plasma secondary to decreased hepatic metabolic degradation of the drug or diminished plasma protein binding capacity due to acidosis, pathologically lowered plasma protein production, or competition with other drugs for protein binding sites. Although rare, some individuals have a lower tolerance to and are supersensitive

to bupivacaine and other amide-type local anesthetics and may rapidly develop signs of toxicity at low doses [*See Overdosage (10)*].

6.2 Adverse Reactions Reported in All Wound Infiltration Clinical Studies

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety of EXPAREL was evaluated in 10 randomized, double-blind, local administration into the surgical site clinical studies involving 823 patients undergoing various surgical procedures. Patients were administered a dose ranging from 66 to 532 mg of EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, constipation, and vomiting.

The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following EXPAREL administration were pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.

The less common/rare adverse reactions (incidence less than 2%) following EXPAREL administration were chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, dizziness postural, paresthesia, syncope, incision site edema, procedural hypertension, procedural hypotension, procedural nausea, muscular weakness, neck pain, pruritus generalized, rash pruritic, hyperhidrosis, cold sweat, urticaria, bradycardia, palpitations, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, ventricular tachycardia, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory depression, respiratory failure, body temperature increased, blood pressure increased, blood pressure decreased, oxygen saturation decreased, urinary retention, urinary incontinence, vision blurred, tinnitus, drug hypersensitivity, and hypersensitivity.

Neurological and Cardiac Adverse Reactions Reported in All Wound Infiltration Clinical Studies

In the EXPAREL wound infiltration studies, adverse reactions with an incidence greater than or equal to 1% in the Nervous System Disorders system organ class following EXPAREL administration were dizziness (6.2%), headache (3.8%), somnolence (2.1%), hypoesthesia (1.5%), and lethargy (1.3%). The adverse reactions with an incidence greater than or equal to 1% in the Cardiac Disorders system organ class following EXPAREL administration were tachycardia (3.9%) and bradycardia (1.6%).

Adverse Reactions Reported in Placebo-Controlled Wound Infiltration Clinical Studies

Adverse reactions with an incidence greater than or equal to 2% reported by patients in clinical studies comparing 8 mL EXPAREL 1.3% (106 mg) to placebo and 20 mL EXPAREL 1.3% (266 mg) to placebo are shown in Table 1.

Table 1: Treatment-Emergent Adverse Reactions (TEAE) with an Incidence Greater than or Equal to 2%: Placebo-Controlled Studies

	STUDY 1[a]		STUDY 2[b]	
	EXPAREL	Placebo	EXPAREL	Placebo
System Organ Class Preferred Term	8 mL/1.3% (106 mg) (N=97) n (%)	(N=96) n (%)	20 mL/1.3% (266 mg) (N=95) n (%)	(N=94) n (%)
Any TEAE	53 (54.6)	59 (61.5)	10 (10.5)	17 (18.1)
Gastrointestinal Disorders	41 (42.3)	38 (39.6)	7 (7.4)	13 (13.8)
Nausea	39 (40.2)	36 (37.5)	2 (2.1)	1 (1.1)
Vomiting	27 (27.8)	17 (17.7)	2 (2.1)	4 (4.3)
Constipation	2 (2.1)	1 (1.0)	2 (2.1)	2 (2.1)
Anal Hemorrhage	0 (0.0)	0 (0.0)	3 (3.2)	4 (4.3)
Painful Defecation	0 (0.0)	0 (0.0)	2 (2.1)	5 (5.3)
Rectal Discharge	0 (0.0)	0 (0.0)	1 (1.1)	3 (3.2)
Nervous System Disorders	20 (20.6)	30 (31.3)	0 (0.0)	0 (0.0)
Dizziness	11 (11.3)	25 (26.0)	0 (0.0)	0 (0.0)
Headache	5 (5.2)	8 (8.3)	0 (0.0)	0 (0.0)
Somnolence	5 (5.2)	1 (1.0)	0 (0.0)	0 (0.0)
Syncope	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin And Subcutaneous Tissue Disorders	8 (8.2)	7 (7.3)	0 (0.0)	0 (0.0)
Pruritus Generalized	5 (5.2)	6 (6.3)	0 (0.0)	0 (0.0)
Pruritus	3 (3.1)	1 (1.0)	0 (0.0)	0 (0.0)
Investigations	5 (5.2)	3 (3.1)	4 (4.2)	3 (3.2)
Alanine Aminotransferase Increased	3 (3.1)	3 (3.1)	1 (1.1)	0 (0.0)
Aspartate Aminotransferase Increased	3 (3.1)	2 (2.1)	0 (0.0)	0 (0.0)
Blood Creatinine Increased	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Body Temperature Increased	0 (0.0)	0 (0.0)	3 (3.2)	3 (3.2)

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women of the effect of bupivacaine on the developing fetus. EXPAREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Bupivacaine hydrochloride (HCl) produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. This does not exclude the use of EXPAREL at term for analgesia [*See Labor and Delivery (8.2)*].

Bupivacaine HCl was administered subcutaneously to rats and rabbits during the period of fetal organogenesis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity.

Administration of bupivacaine HCl to rats during pregnancy and lactation resulted in decreased offspring survival.

8.2 Labor and Delivery

Bupivacaine hydrochloride is contraindicated for obstetrical paracervical block anesthesia.

Local anesthetics rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity [*See Clinical Pharmacology (12.3)*]. The incidence and degree of toxicity depend upon the procedure performed, the type, and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

8.3 Nursing mothers

Bupivacaine has been reported to be excreted to some extent in human milk, suggesting that the nursing infant could be theoretically exposed to a dose of the drug. Because of the potential for serious adverse reactions in nursing infants from bupivacaine, a decision should be made whether to discontinue nursing or not administer EXPAREL, taking into account the importance of the drug to the mother.

8.4 Pediatric use

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

8.5 Geriatric use

Of the total number of patients in the EXPAREL wound infiltration clinical studies (N=823), 171 patients were greater than or equal to 65 years of age and 47 patients were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients. Clinical experience with EXPAREL has not identified differences in efficacy or safety between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

System Organ Class Preferred Term	STUDY 1[a] EXPAREL 8 mL/1.3% (106 mg) (N=97) n (%)	STUDY 1[a] Placebo (N=96) n (%)	STUDY 2[b] EXPAREL 20 mL/1.3% (266 mg) (N=95) n (%)	STUDY 2[b] Placebo (N=94) n (%)
General Disorders And Administration Site Conditions	4 (4.1)	0 (0.0)	1 (1.1)	1 (1.1)
Feeling Hot	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	2 (2.1)	0 (0.0)	1 (1.1)	1 (1.1)
Infections And Infestations	2 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)
Fungal Infection	2 (2.1)	1 (1.0)	0 (0.0)	0 (0.0)
Injury, Poisoning And Procedural Complications	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Post Procedural Swelling	2 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism And Nutrition Disorders	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)
Decreased Appetite	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)

[a] Study 1: Bunionectomy
[b] Study 2: Hemorrhoidectomy
At each level of summation (overall, system organ class, preferred term), patients are only counted once.
Preferred terms are included where at least 2% of patients reported the event in any treatment group.
TEAE = treatment-emergent adverse event.

7. DRUG INTERACTIONS

EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e., 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection. EXPAREL must not be diluted with water or other hypotonic agents as it will result in disruption of the liposomal particles.

EXPAREL should not be admixed with lidocaine or other non-bupivacaine-based local anesthetics.

EXPAREL may be locally administered after at least 20 minutes following local administration of lidocaine.

EXPAREL should not be admixed with other drugs prior to administration.

In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients. Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to bupivacaine may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection of EXPAREL.

8.6 Hepatic Impairment

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

8.7 Renal Impairment

Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Care should be taken in dose selection of EXPAREL.

10. OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma concentrations encountered during therapeutic use of local anesthetics or to unintended intravascular injection of local anesthetic solution [*See Warnings and Precautions (5) and Adverse Reactions (6)*].

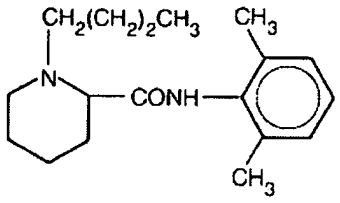
In the clinical study program, maximum plasma concentration (C_{max}) values of approximately 34,000 ng/mL were reported and likely reflected inadvertent intravascular administration of EXPAREL or systemic absorption of EXPAREL at the surgical site. The plasma bupivacaine measurements did not discern between free and liposomal-bound bupivacaine making the clinical relevance of the reported values uncertain; however, no discernable adverse events or clinical sequelae were observed in these patients.

11. DESCRIPTION

EXPAREL is a sterile, non-pyrogenic white to off-white preservative-free aqueous suspension of multivesicular liposomes (DepoFoam® drug delivery system) containing bupivacaine. Bupivacaine is present at a concentration of 13.3 mg/mL. After injection of EXPAREL into soft tissue, bupivacaine is released from the multivesicular liposomes over a period of time.

11.1 Active Ingredient

Bupivacaine is related chemically and pharmacologically to the amide-type local anesthetics. It is a homologue of mepivacaine and is related chemically to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino, or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage. Chemically, bupivacaine is 1-butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide with a molecular weight of 288.4. Bupivacaine has the following structural formula:



Bupivacaine is present in EXPAREL at a concentration of 13.3 mg/mL.

11.2 Lipid Formulation

The median diameter of the liposome particles ranges from 24 to 31 μm. The liposomes are suspended in a 0.9% sodium chloride solution. Each vial contains bupivacaine at a nominal concentration of 13.3 mg/mL. Inactive ingredients and their nominal concentrations are: cholesterol, 4.7 mg/mL; 1, 2-dipalmitoyl-sn-glycero-3 phospho-rac-(1-glycerol) (DPPG), 0.9 mg/mL; tricaprylin, 2.0 mg/mL; and 1, 2-dierucoylphosphatidylcholine (DEPC), 8.2 mg/mL. The pH of EXPAREL is in the range of 5.8 to 7.4.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Local anesthetics block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.2 Pharmacodynamics

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems. At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conductivity and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after accidental intravascular injection of bupivacaine.

soluble, non-ionized drugs such as bupivacaine readily enter the fetal blood from the maternal circulation.

Metabolism

Amide-type local anesthetics, such as bupivacaine, are metabolized primarily in the liver via conjugation with glucuronic acid. Pipecolylxylidine (PPX) is the major metabolite of bupivacaine; approximately 5% of bupivacaine is converted to PPX. Elimination of drug depends largely upon the availability of plasma protein binding sites in the circulation to carry it to the liver where it is metabolized.

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic disease. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics.

Excretion

After bupivacaine has been released from EXPAREL and is absorbed systemically, bupivacaine excretion is expected to be the same as for other bupivacaine formulations.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Only 6% of bupivacaine is excreted unchanged in the urine.

Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Acidifying the urine hastens the renal elimination of local anesthetics. Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of renal disease, factors affecting urinary pH, and renal blood flow.

Specific Populations

Hepatic Impairment

The effects of decreased hepatic function on bupivacaine pharmacokinetics following administration of EXPAREL were studied in patients with moderate hepatic impairment. Consistent with the hepatic clearance of bupivacaine, mean plasma concentrations were higher in patients with moderate hepatic impairment than in the healthy control volunteers with approximately 1.5- and 1.6-fold increases in the mean values for C_{max} and the area under the curve (AUC), respectively.

Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, these drugs should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations [*See Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].

Renal Impairment

Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Care should be taken in dose selection of EXPAREL [*See Use in Specific Populations (8.7)*].

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors, and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.

12.3 Pharmacokinetics

Local infiltration of EXPAREL results in significant systemic plasma levels of bupivacaine which can persist for 96 hours [*See Warnings and Precautions (5.2)*]. Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy.

Absorption

The rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site.

Pharmacokinetic parameters of EXPAREL after local administration were evaluated following surgical procedures. Descriptive statistics of pharmacokinetic parameters of representative EXPAREL doses in each study are provided in Table 2.

Table 2: Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of EXPAREL

	EXPAREL	
	Bunionectomy 106 mg (8 mL)	**Hemorrhoidectomy 266 mg (20 mL)**
	(N=26)	**(N=25)**
C_{max} (ng/mL)	166 (92.7)	867 (353)
T_{max} (h)	2	0.5
$AUC_{(0-t)}$ (h×ng/mL)	5864 (2038)	16,867 (7868)
$AUC_{(inf)}$ (h×ng/mL)	7105 (2283)	18,289 (7569)
$t_{½}$ (h)	34.1 (17.0)	23.8 (39.4)

Note: Arithmetic mean (standard deviation) except T_{max} (median).

Distribution

After bupivacaine has been released from EXPAREL and is absorbed systemically, bupivacaine distribution is expected to be the same as for any bupivacaine HCl solution formulation.

Local anesthetics including bupivacaine are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Local anesthetics including bupivacaine appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid

Age

Various pharmacokinetic parameters of the local anesthetics such as bupivacaine can be significantly altered by the age of the patient.

In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients.

Bupivacaine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection of EXPAREL [*See Use in Specific Populations (8.5)*].

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies in animals of most local anesthetics, including bupivacaine, to evaluate the carcinogenic potential have not been conducted. Mutagenic potential and the effect on fertility have not been determined. There is no evidence from human data that bupivacaine may be carcinogenic or mutagenic or that it impairs fertility.

14. CLINICAL STUDIES

The efficacy of EXPAREL was compared to placebo in two multicenter, randomized, double-blinded clinical trials. One trial evaluated the treatments in patients undergoing bunionectomy; the other trial evaluated the treatments in patients undergoing hemorrhoidectomy. EXPAREL has not been demonstrated to be safe and effective in other procedures.

14.1 Bunionectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of 106 mg EXPAREL in 193 patients undergoing bunionectomy. The mean age was 43 years (range 18 to 72). Study medication was administered directly into the wound at the conclusion of the surgery, prior to wound closure. Pain intensity was rated by the patients on a 0 to 10 numeric rating scale (NRS) out to 72 hours. Postoperatively, patients were allowed rescue medication (5 mg oxycodone/325 mg acetaminophen orally every 4 to 6 hours as needed) or, if that was insufficient within the first 24 hours, ketorolac (15 to 30 mg IV). The primary outcome measure was the area under the curve (AUC) of the NRS pain intensity scores (cumulative pain scores) collected over the first 24 hour period. There was a significant treatment effect for EXPAREL compared to placebo.

In this clinical study, EXPAREL demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours. The difference in mean pain intensity between treatment groups occurred only during the first 24 hours following study drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between EXPAREL and placebo treatments on mean pain intensity.

14.2 Hemorrhoidectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of 266 mg EXPAREL in 189 patients undergoing hemorrhoidectomy. The mean age was 48 years (range 18 to 86). Study medication was administered directly into the wound (greater than or equal to 3 cm) at the conclusion of the surgery. Pain intensity was rated by the patients on a 0 to 10 NRS at multiple time points up to 72 hours. Postoperatively, patients were allowed rescue medication (morphine sulfate 10 mg intramuscular every 4 hours as needed). The primary outcome measure was the AUC of the NRS pain intensity scores (cumulative pain scores) collected over the first 72 hour period. There was a significant treatment effect for EXPAREL compared to placebo.

In this clinical study, EXPAREL demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours. The difference in mean pain intensity between treatment groups occurred only during the first 24 hours following study drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between EXPAREL and placebo treatments on mean pain intensity; however, there was an attendant decrease in opioid consumption, the clinical benefit of which was not demonstrated.

16. HOW SUPPLIED/STORAGE AND HANDLING

EXPAREL (bupivacaine liposome injectable suspension) is available in single-use vials for infiltration.

10 mL single use vial, 1.3% (13.3 mg/mL) packaged in cartons of 10 (NDC 65250-133-10)

20 mL single use vial, 1.3% (13.3 mg/mL) packaged in cartons of 10 (NDC 65250-266-20)

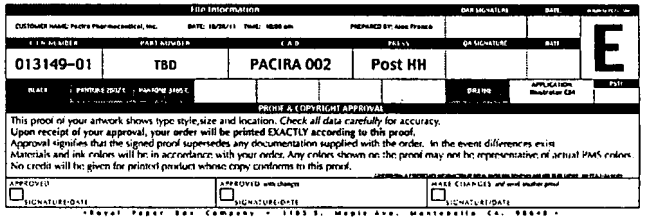
Different formulations of bupivacaine are not bioequivalent even if the milligram strength is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL.

Storage

EXPAREL vials should be stored refrigerated between 2°C to 8°C (36°F to 46°F). EXPAREL may be held at a controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to one month in sealed, intact (unopened) vials. Vials should not be re-refrigerated. As a convenience to the hospital pharmacist, each vial label includes space to record the date when the vial has been removed from refrigeration.

EXPAREL should not be frozen as reflected by the temperature indicator or exposed to high temperatures (greater than 40°C or 104°F) for an extended period. Do not administer EXPAREL if it is suspected of having been frozen as reflected by the temperature indicator or exposed to high temperatures.

Check the freeze indicator and discard product if it has been triggered. The freeze indicator turns from green to white when exposed to freezing temperatures.



NDC 65250-133-10

EXPAREL

(bupivacaine liposome injectable suspension)

1.3%

133 mg/10mL (13.3 mg/mL)

For infiltration ONLY. Not for any other route of administration.

Storage: Protect from freezing.

EXPAREL

(bupivacaine liposome injectable suspension)

1.3%

133 mg/10mL (13.3 mg/mL)

For infiltration ONLY. Not for any other route of administration.

Part No.: XXXXXXX

NO COAT

NDC 65250-133-10

EXPAREL

(bupivacaine liposome injectable suspension)

1.3%

133 mg/10mL (13.3 mg/mL)

For infiltration ONLY. Not for any other route of administration.

Contents: Each 10 mL vial contains 133 mg of bupivacaine free base

Usual Dosage: See package insert. Do not substitute for or with other formulations containing bupivacaine or bupivacaine HCl.

10 Vials per Carton

Rx Only

EXPAREL

(bupivacaine liposome injectable suspension)

1.3%

133 mg/10mL (13.3 mg/mL)

For infiltration ONLY. Not for any other route of administration.

Part No.: XXXXXXX

NO COAT

EXPAREL

(bupivacaine liposome injectable suspension)

1.3%

133 mg/10mL (13.3 mg/mL)

For infiltration ONLY. Not for any other route of administration.

Storage: Protect from freezing. Refrigerate 2°C to 8°C (36°F to 46°F). Do not filter. Product can be stored at controlled room temperatures not exceeding 25°C (77°F) for up to 30 days prior to use. Store vials in outer carton.

Single use vial: discard any unused portion.

See package insert for additional storage information.

Manufactured by:

PACIRA

10450 Science Center Drive

San Diego, CA 92121

LOT

EXP

Handling

- Vials of EXPAREL should be inverted to re-suspend the particles immediately prior to withdrawal from the vial. Multiple inversions may be necessary to re-suspend the particles if the contents of the vial have settled.
- Vials should be visually inspected before use.
- Do not filter.
- Do not heat before use.
- Do not autoclave.
- EXPAREL should be administered with a 25 gauge or larger bore needle.
- EXPAREL can be administered undiluted or diluted up to 0.89 mg/mL (i.e. 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection.
- Following withdrawal from the vial, EXPAREL may be stored at controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 4 hours prior to administration.
- Discard any unused portion in an appropriate manner.

17. PATIENT COUNSELING INFORMATION

Patients should be informed in advance that bupivacaine-containing products can cause temporary loss of sensation or motor activity in the area infiltrated. Physicians should discuss adverse reactions in the EXPAREL prescribing information with their patients.

Pacira Pharmaceuticals, Inc.

San Diego, CA 92121 USA

Patent Numbers:

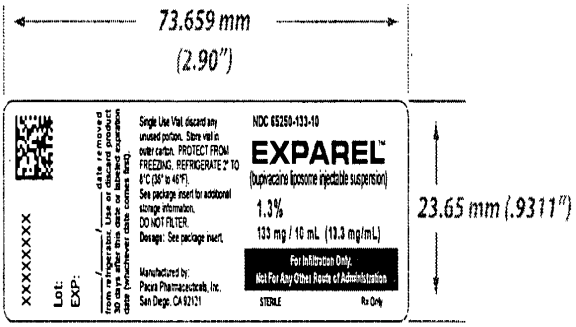
6,132,766

5,766,627

5,891,467

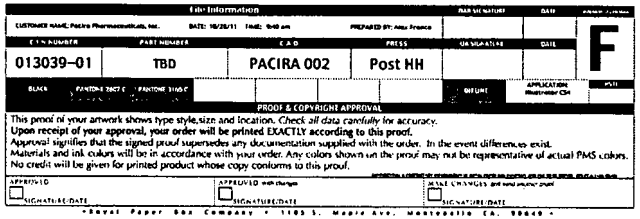
Trademark of Pacira Pharmaceuticals, Inc.

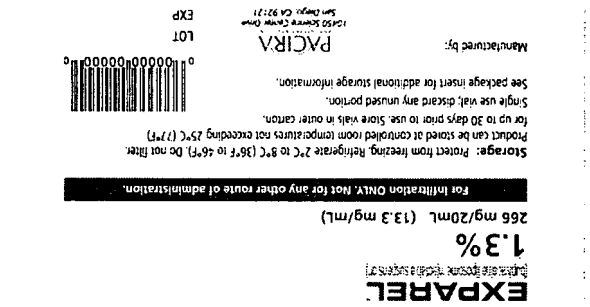
PACIRA
PHARMACEUTICALS, INC.

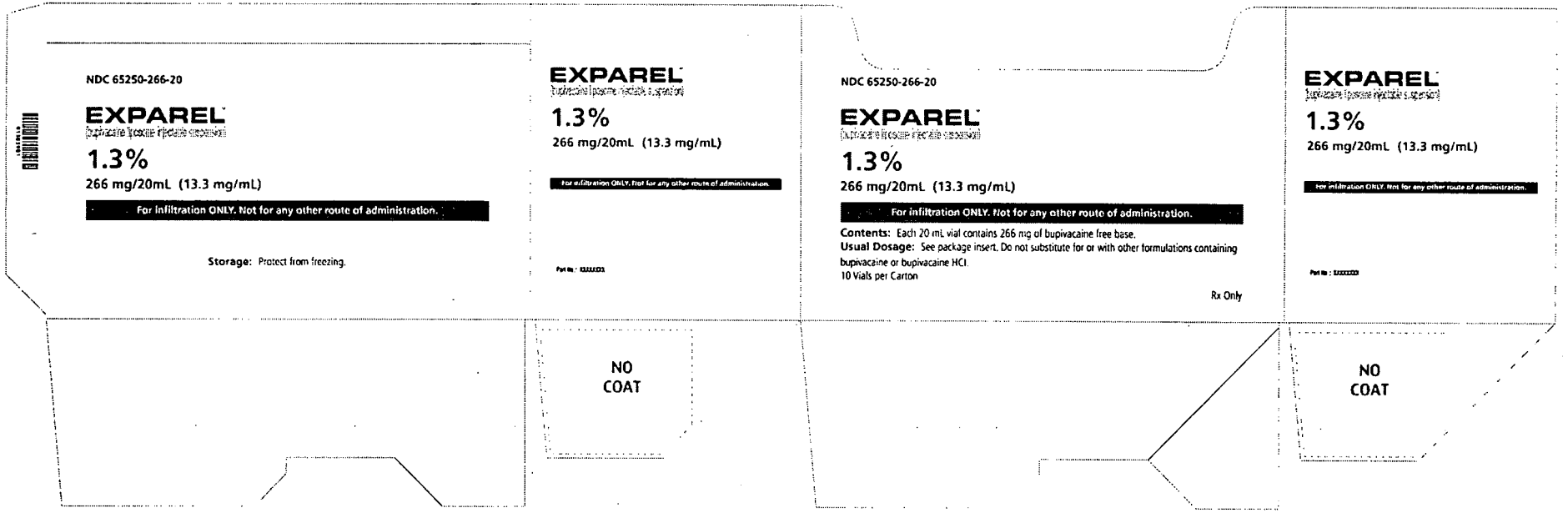


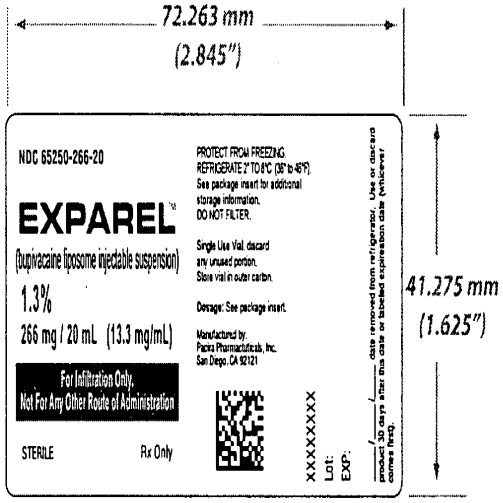
Pacira Pharmaceuticals, Inc. EXPAREL 10 mL	CCL LABEL Healthcare Solutions Group 576 College Commerce Way Upland, CA 91786 909-608-2260	CONFIDENTIAL INFORMATION THIS DRAWING CONTAINS CONFIDENTIAL INFORMATION THAT IS THE PROPERTY OF CCL LABEL. DO NOT DUPLICATE WITHOUT PRIOR APPROVAL.
	TOLERANCES UNLESS OTHERWISE SPECIFIED - PRINT TO DIE: ± .031" - PRINT TO PRINT: ± .031"	SIZE: N/A · DRAWN BY: Ramon Delgado · DWG NO.: Ramon Delgado · REV: 11 SCALE: N/A · Date: 10/28/11 · SHEET

Reference ID: 3036637









Pacira Pharmaceuticals, Inc.

EXPAREL 20 mL

Reference ID: 3036637

CCL LABEL
Healthcare Solutions Group

576 College Commerce Way
Upland, CA 91786
909-608-2260

TOLERANCES UNLESS OTHERWISE SPECIFIED

- PRINT TO DIE: ± .031"
- PRINT TO PRINT: ± .031"

CONFIDENTIAL INFORMATION

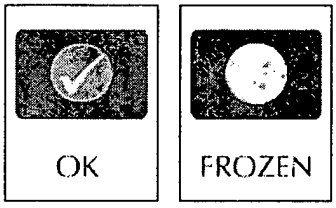
SIZE	DRAWN BY:	DWG NO.	REV
N/A	Ramon Delgado	Ramon Delgado	11

SCALE	Date	SHEET
N/A	10/28/11	

Pull and Check Immediately
Reinsert after Inspection

Compare the Indicator to the Pictures Below.

Do Not Use the Product if the Indicator has been Frozen.



TEMPTIME
www.temptimecorp.com

Reference ID: 3036637

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
10/28/2011

EXHIBIT D

Quick Links: Skip to main page content Skip to Search Skip to Topics Menu Skip to Common Links

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Search results from the "OB_Rx" table for query on "016964."

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MARCAINE HYDROCHLORIDE
Applicant:	HOSPIRA
Strength:	0.25%
Application Number:	N016964
Product Number:	001
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE; EPINEPHRINE BITARTRATE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MARCAINE HYDROCHLORIDE W/ EPINEPHRINE
Applicant:	HOSPIRA
Strength:	0.25%;0.0091MG/ML
Application Number:	N016964
Product Number:	004
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MARCAINE HYDROCHLORIDE PRESERVATIVE FREE
Applicant:	HOSPIRA
Strength:	0.5%
Application Number:	N016964
Product Number:	005
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MARCAINE HYDROCHLORIDE
Applicant:	HOSPIRA
Strength:	0.5%
Application Number:	N016964
Product Number:	006
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE; EPINEPHRINE BITARTRATE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MARCAINE HYDROCHLORIDE W/ EPINEPHRINE PRESERVATIVE FREE
Applicant:	HOSPIRA
Strength:	0.5%;0.0091MG/ML
Application Number:	N016964
Product Number:	007
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE; EPINEPHRINE BITARTRATE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MARCAINE HYDROCHLORIDE W/ EPINEPHRINE
Applicant:	HOSPIRA
Strength:	0.5%;0.0091MG/ML
Application Number:	N016964
Product Number:	008
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MARCAINE HYDROCHLORIDE PRESERVATIVE FREE
Applicant:	HOSPIRA
Strength:	0.75%
Application Number:	N016964

Product Number:	009
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE; EPINEPHRINE BITARTRATE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MARCAINE HYDROCHLORIDE W/ EPINEPHRINE PRESERVATIVE FREE
Applicant:	HOSPIRA
Strength:	0.75%;0.0091MG/ML
Application Number:	N016964
Product Number:	010
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MARCAINE HYDROCHLORIDE PRESERVATIVE FREE
Applicant:	HOSPIRA
Strength:	0.25%
Application Number:	N016964
Product Number:	012
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE; EPINEPHRINE BITARTRATE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	MARCAINE HYDROCHLORIDE W/ EPINEPHRINE PRESERVATIVE FREE
Applicant:	HOSPIRA
Strength:	0.25%;0.0091MG/ML
Application Number:	N016964
Product Number:	013
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through November, 2011

Patent and Generic Drug Product Data Last Updated: December 15, 2011

Quick Links: Skip to main page content Skip to Search Skip to Topics Menu Skip to Common Links

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Search results from the "OB_Rx" table for query on "018053."

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	BUPIVACAINE HYDROCHLORIDE
Applicant:	HOSPIRA
Strength:	0.5%
Application Number:	N018053
Product Number:	001
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	BUPIVACAINE HYDROCHLORIDE
Applicant:	HOSPIRA
Strength:	0.25%
Application Number:	N018053
Product Number:	002
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	BUPIVACAINE HYDROCHLORIDE
Applicant:	HOSPIRA
Strength:	0.75%
Application Number:	N018053
Product Number:	003
Approval Date:	Approved Prior to Jan 1, 1982
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Quick Links: Skip to main page content Skip to Search Skip to Topics Menu Skip to Common Links

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Search results from the "OB_Rx" table for query on "018692."

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE
Dosage Form;Route:	INJECTABLE; SPINAL
Proprietary Name:	MARCAINE
Applicant:	HOSPIRA
Strength:	0.75%
Application Number:	N018692
Product Number:	001
Approval Date:	May 4, 1984
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through November, 2011

Patent and Generic Drug Product Data Last Updated: December 19, 2011

Quick Links: Skip to main page content Skip to Search Skip to Topics Menu Skip to Common Links

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Search results from the "OB_Rx" table for query on "022046."

Active Ingredient:	BUPIVACAINE HYDROCHLORIDE; EPINEPHRINE BITARTRATE
Dosage Form;Route:	INJECTABLE; INJECTION
Proprietary Name:	BUPIVACAINE HYDROCHLORIDE W/EPINEPHRINE
Applicant:	HOSPIRA
Strength:	0.5%;0.0091MG/ML
Application Number:	N022046
Product Number:	001
Approval Date:	Jul 13, 1983
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AP**
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

- Orange Book Data - **Monthly**
- Generic Drug Product Information & Patent Information - **Daily**
- Orange Book Data Updated Through November, 2011
- Patent and Generic Drug Product Data Last Updated: December 15, 2011

EXHIBIT E

US006132766A

United States Patent [19]

Sankaram et al.

[11] Patent Number: 6,132,766

[45] Date of Patent: *Oct. 17, 2000

[54] MULTIVESICULAR LIPOSOMES WITH CONTROLLED RELEASE OF ENCAPSULATED BIOLOGICALLY ACTIVE SUBSTANCES

[75] Inventors: **Mantripragada Bhima Sankaram**, San Diego; **Sinil Kim**, Solana Beach, both of Calif.

[73] Assignee: **SkyePharma Inc.**, San Diego, Calif.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **09/045,236**

[22] Filed: **Mar. 20, 1998**

Related U.S. Application Data

[62] Division of application No. 08/898,017, Jul. 21, 1997, abandoned, which is a continuation of application No. 08/473,013, Jun. 6, 1995, abandoned, which is a continuation of application No. 08/153,657, Nov. 16, 1993, abandoned.

[51] **Int. Cl.**[7] **A61K 9/127**

[52] **U.S. Cl.** **424/450**; 424/417; 424/DIG. 8; 264/4.1; 264/4.3; 264/4.6

[58] **Field of Search** 424/1.21, 9.321, 424/9.51, 417, 450; 264/4.1, 4.3, 4.6; 436/829; 935/54

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,078,052	3/1978	Papahadjopoulos .	
4,089,801	5/1978	Schneider .	
4,145,410	5/1979	Sears .	
4,224,179	9/1980	Schneider .	
4,235,871	11/1980	Papahadjopoulos et al. .	
4,310,506	1/1982	Baldeschwieler et al. .	
4,394,372	7/1983	Taylor .	
4,522,803	6/1985	Lenk et al. .	
4,588,578	5/1986	Fountain et al. .	
4,599,227	7/1986	Dees et al. .	
4,610,868	9/1986	Fountain et al. .	
4,752,425	7/1988	Martin et al. .	
4,769,250	9/1988	Forssen .	
4,771,612	1/1988	Janoff	424/1.1
4,781,871	11/1988	West, III et al. .	
4,920,016	4/1990	Allen et al. .	
4,975,282	12/1990	Cullis	424/450
5,000,959	3/1991	Iga et al. .	
5,021,200	6/1991	Vanlerberghe et al. .	
5,077,056	12/1991	Bally et al. .	
5,204,112	4/1993	Hope et al. .	
5,211,955	5/1993	Legros et al. .	
5,334,381	8/1994	Unger et al.	424/9
5,334,391	8/1994	Clark et al.	424/450

FOREIGN PATENT DOCUMENTS

0315467	10/1989	European Pat. Off. .
2050287	1/1991	United Kingdom .

OTHER PUBLICATIONS

"Topology of Multivesicular Liposomes, a Model Biliquid Foam, "*Langmuir*12;4704–4708, 1996, by M.S. Spencer et al.

Crommelin, Internat. J. Pharmaceutics 16 (1983) p.79.

Huang, Biochemistry, 8:334–352, 1969, "Studies on Phosphatidylcholine Vesicles formation and Physical Characteristics."

(List continued on next page.)

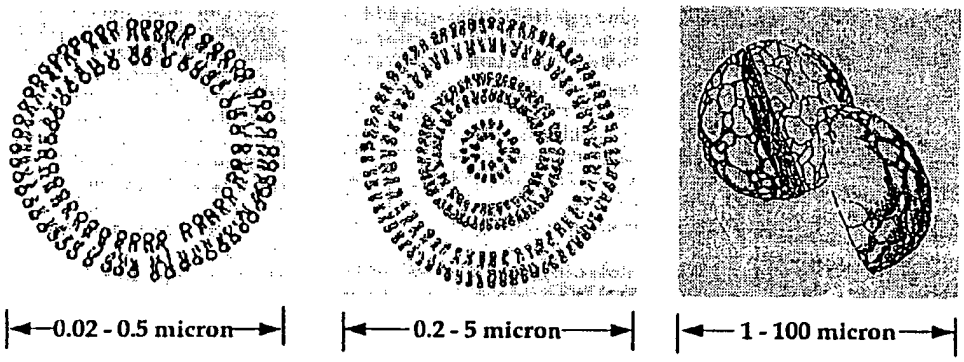
Primary Examiner—Gollamudi S. Kishore

Attorney, Agent, or Firm—Fish & Richardson P.C.

[57] **ABSTRACT**

A multivesicular liposome composition containing at least one acid other than a hydrohalic acid and at least one biologically active substance, the vesicles having defined size distribution, adjustable average size, internal chamber size and number, provides a controlled release rate of the biologically active substance from the composition. A process for making the composition features addition of a non-hydrohalic acid effective to sustain and control the rate of release of an encapsulated biologically active substance from the vesicles at therapeutic levels in vivo.

35 Claims, 1 Drawing Sheet



OTHER PUBLICATIONS

Bangham , A.V. Mol. Bio., 13–238–252, 1965, "Diffusion of univalent ions across the lamellae of swollen phospholipids."

Szoka, et al., Ann. Rev. Biophys. Bioeng., 9:465–508, 1980, "Comparative properties and methods of preparation of lipid vesicles (liposomes) . "

Shakiba, et al., Investigative ophthalmology and visual Science, 34(10) :2903–10, 1993 Sep., "Evaluation of retinal toxicity and liposome encapsulation of the Anti–CMV Drug 2'–nor–cyclic GMP."

Frucht–Perry, et al., Cornea, 11(5) :393–7, 1992 Sep., "Fibrin–enmeshed tobramycin liposomes: single application topical therapy of pseudomonas..."

Assil, et al., Investigative Ophthalmology and Visual Science, 32(13) :3216–20, 1991 Dec., "Tobramycin liposomes. Single subconjunctival therapy of ...".

Assil, et al., Investigative Ophthalmology and Visual Science, 32(11) :2891–7, 1991 Oct., Lipsome suppression of proliferative vitreoretinopathy. Rabbit....

Turski, et al., Magnetic Resonance in Medicine, 7(2) :184–96, 1988 Jun., "Magnetic resonance imaging of rabbit brain after intracarotid injection...".

Skuta, et al., American Journal of Ophthalmology, 103(5) : 714–16, May 15, 1987, "Filtering surgery in owl monkeys treated with the antimetabolite...".

Assil, et al., Archives of Ophthalmology, 105(3) :400–3, 1987 Mar., "Multivesicular liposomes. Sustained release of the antimetabolite...".

Barbet, et al., *Biochimica et Biophysica Acta*, 772(3) : 347–56, May 30, 1984, "Weat acid–induced release of liposome–encapsulated carboxyflourescein".

Kim et al., Biochim. Biophys. Acta, 646:1, 1981, "Preparation of cell–size unilamellar liposomes with high captured volume and defined size...".

Kim, et al., Biochim. Biophys. Acta, 728:339–348, 1983, "Preparation of multivesicular liposomes".

Kim, et al., Biochim. Biophys. Acta, 793:801, 1985, "Preparation of multilamellar vesicles of defined sized–distribution by solvent–spherule...".

Kim, et al., Cancer Treat. Rep., 71:705–711, 1987, "Multivesicular liposomes containing cytarabine entrapped in the presence of ...".

Kim, et al., Cancer Research, 47:3935–3937, 1987, "Multivesicular Liposomes Containing 1–B–D–arabinofuranosyxcytosine for slow–release intrathecal therapy".

Kim, et al., Cancer Treat Rep., 71:447–450, 1987, "Multivesicular liposomes containing cytosine arabinoside for slow–release...".

Kim, et al., Cancer Chemother Pharmacology, 19:307–310, 1987, "Modulation of the peritoneal clearance of liposomal ara–C by blank liposomes".

Roy, et al., Cancer Chemother. Pharm., 28:105–108, 1991, "Multivesicular liposomes containing bleomycin for subcutaneous administration".

Kim, et al., Reg. Cancer Treat., 2:170–173, 1989, "Intratumoral Chemotherapy with multivesicular liposomes containing 1–b–D–arabino...".

Kim, et al., J. Inf. Dis., 162:750–752, 1990, "Multivesicular liposomes for CSF delivery of retroviral agent DDC".

Chamberlain, et al., Archives of Neurol, 50(3) :261–264, 1993, "Treatment of leptomeningeal metastasis with intraventricular administration of ...".

Chatelut, et al., Cancer Them. Pharmacol., 32:179–182, 1993 "A slow–release methotrexate formulation for inrathecal chemotherapy".

Russack, et al., Ann. Neurol., 34:108–112, 1993, "Quantitative cerebrospinal fluid cytology in patients receiving intracavitary chemotherapy".

Kim, et al., J. Clin. Oncol., 11:2186–2193, 1993,"Extended cerebrospinal–fluid cytarabine exposure following intrathecal administration of DTC 101".

Kim, Drugs, 46:618–630, 1993, "Liposomes as carriers of cancer chemotherapy: a review".

Kim, Kim, Kim, Cancer Chemother. Pharmacol., 33:187–190, 1993, "Extended–release formulation of morphine for subcutaneous administration".

Ishii, Liposome Technology, 1:111–121, 1993, "Production and size Control of large unilamellar liposomes by emulsification".

Cullis, et al., Phospholipids and Cellular Regulation, 1:65–123, 1985, "Structural properties and functional roles of phospholipids in...".

Bonetti, et al., Cancer Chemotherapy and Pharmacology, In Press, 1993, "An Extended–release formulation of methotrexate for subcutaneous...".

Kim, et al., Cancer Res., 53;1596–1598, 1993, "Prolongation of drug action in CSF by encapsulation into Depofoam".

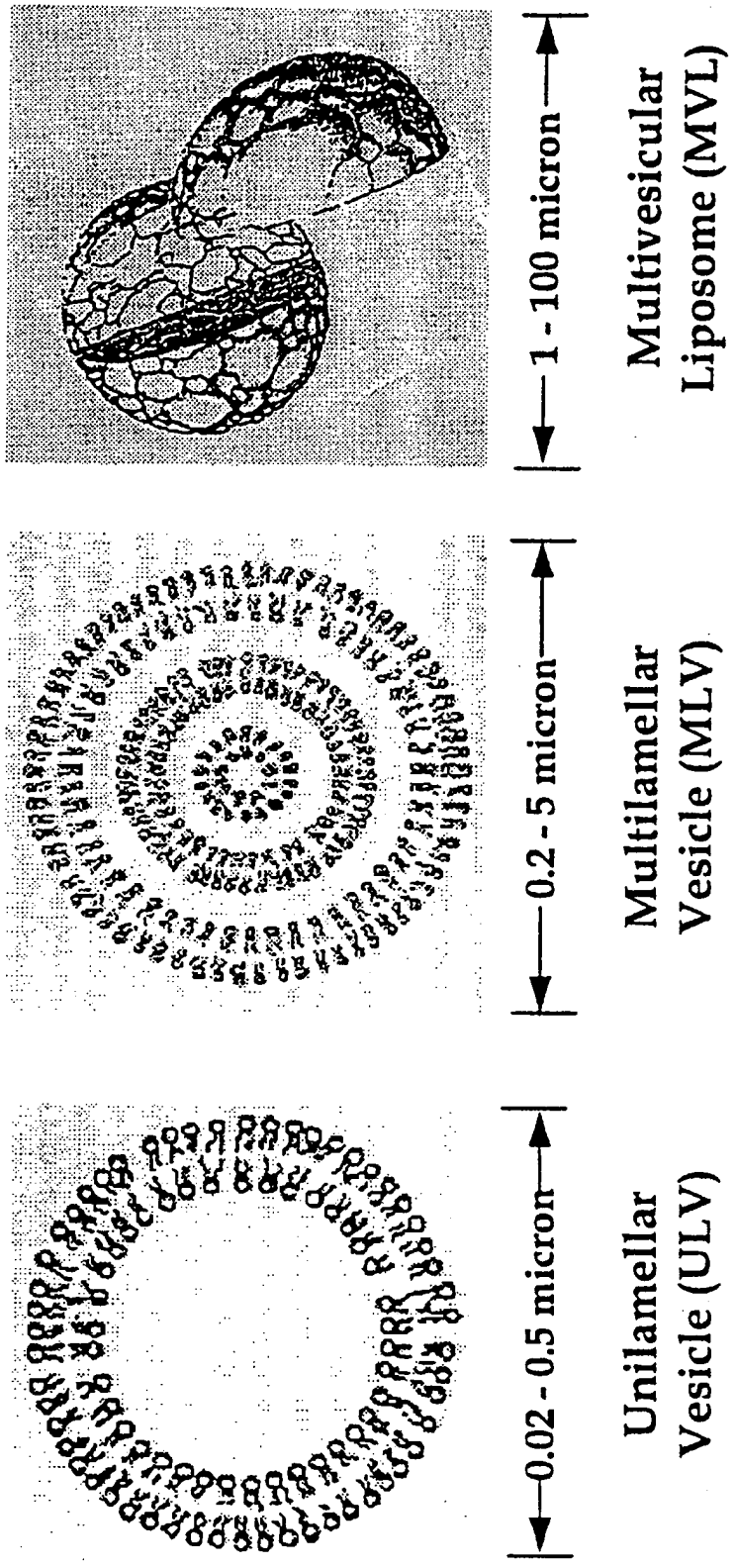

1 - 100 micron
Multivesicular Liposome (MVL)
0.2 - 5 micron
Multilamellar Vesicle (MLV)
0.02 - 0.5 micron
Unilamellar Vesicle (ULV)

Figure 1

MULTIVESICULAR LIPOSOMES WITH CONTROLLED RELEASE OF ENCAPSULATED BIOLOGICALLY ACTIVE SUBSTANCES

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 08/898,017, filed Jul. 21, 1997, now abandoned, which is a continuation of U.S. patent application Ser. No. 08/473,013, filed Jun. 6, 1995, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/153,657, filed Nov. 16, 1993, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to compositions of multivesicular liposomes useful as a drug delivery system and processes for their manufacture.

2. Description of Related Art

Optimal treatment with many drugs requires maintenance of a drug level for an extended period of time. For example, optimal anti-cancer treatment with cell cycle-specific antimetabolites requires maintenance of a cytotoxic drug level for a prolonged period of time. The half-life of many drugs after an intravenous (IV), subcutaneous (SC), intraperitoneal (IP), intraarterial (IA), intramuscular (IM), intrathecal (IT), or epidural dose is very short, being in the range of a fraction of an hour to a few hours. Cytarabine is a highly schedule-dependent anti-cancer drug. Because this drug kills cells only when they are making DNA, prolonged exposure at therapeutic concentration of the drug is required for optimal cell kill. To achieve optimal cancer cell kill with a cell cycle phase-specific drug like cytarabine, two major requirements need to be met: irreversible harm to the host; and second, the tumor must be exposed for a sufficient length of time so that all or most of the cancer cells have attempted to synthesize DNA in the presence of cytarabine.

An example of another class of drugs that are schedule-dependent is the class of aminoglycoside antibiotics. For instance, amikacin is an aminoglycoside antibiotic that has clinically significant activity against strains of both gram negative and gram positive bacteria, but has a serum half-life of about two to three hours. Yet in current practice, the drug is normally administered by intravenous or intramuscular routes once or twice a day. The most commonly used clinical dose is 15 mg/Kg/day, which is equivalent to a maximum recommended daily dose of 1 g per day.

For infections such as those confined to a local region of soft tissue or bone, an implantable drug depot with sustained release properties would be advantageous, both to increase local levels of the drug in the affected tissue and to reduce or avoid the systemic toxicity of the free drug.

Thus, new and better methods for sustained release delivery of drugs in the treatment of disease are needed. The present invention meets this need by providing compositions of multivesicular liposomes useful as a sustained release drug delivery system and a process for their manufacture.

Multivesicular liposomes (MVL), first reported by Kim, et al. (*Biochim, Biophys. Acta,* 728:339–348, 1983), are uniquely different from other lipid-based drug delivery systems such as unilamellar (Huang, *Biochemistry,* 8:334–352, 1969; Kim, et al., *Biochim. Biophys. Acta,* 646:1–10, 1981) and multilamellar (Bangham, et al., *J Mol. Bio.,* 13:238–252, 1965) liposomes. The main structural difference is that in contrast to unilamellar liposomes (also known as unilamellar vesicles, or "ULV"), multivesicular liposomes (MVL) contain multiple aqueous chambers per particle. In contrast to multilamellar liposomes (also known as multilamellar vesicles or "MLV"), the multiple aqueous chambers in multivesicular liposomes are non-concentric. The structural differences between unilamellar, multilamellar, and multivesicular liposomes are illustrated in FIG. 1.

Because of the similarity in acronyms, multivesicular liposomes (MVL) are frequently confused with multilamellar liposomes (MLV). Nevertheless, the two entities are entirely distinct from each other. The structural and functional characteristics of MVL are not directly predictable from current knowledge of ULV and MLV. As described in the book edited by Jean R. Philippot and Francis Schuber (*Liposomes as Tools in Basic Research and Industry,* CRC press, Boca Raton, Fla.,1995, page 19), MVL are bounded by an external bilayer membrane shell, but have a very distinctive internal morphology, which may arise as a result of the special method employed in the manufacture. Topologically, multivesicular liposomes (MVL) are defined as liposomes containing multiple non-concentric chambers within each liposome particle, resembling a "foam-like" matrix; whereas multilamellar vesicles (MLV) contain multiple concentric chambers within each liposome particle, resembling the "layers of an onion".

The presence of internal membranes distributed as a network throughout MVL may serve to confer increased mechanical strength to the vesicle, while still maintaining a high volume:lipid ratio compared with MLV. The multivesicular nature of MVL also indicates that, unlike for ULV, a single breach in the external membrane of a MVL will not result in total release of the internal aqueous contents. Thus, both structurally and functionally the MVL are unusual, novel and distinct from all other types of liposomes. As a result, the functional properties of MVL are not predictable based on the prior art related to conventional liposomes such as ULV and MLV.

The prior art describes a number of techniques for producing ULV and MLV (for example, U.S. Pat. Nos. 4,522,803 to Lenk; 4,310,506 to Baldeschwieler; 4,235,871 to Papahadjopoulos; 4,224,179 to Schneider; 4,078,052 to Papahadjopoulos; 4,394,372 to Taylor; 4,308,166 to Marchetti; 4,485,054 to Mezei; and 4,508,703 to Redziniak). The prior art also describes methods for producing MVL (Kim, et al., *Biochim. Biophys. Acta,* 728:339–348, 1983). For a comprehensive review of various methods of ULV and MLV preparation, refer to Szoka, et al., *Ann. Rev. Biophys. Bioeng.*, 9:465–508, 1980.

In the method of Kim, et al. (*Biochim. Biophys. Acta,* 728:339–348, 1983), the pharmaceutical utility of MVL encapsulating small therapeutic molecules, such as cytosine arabinoside or cytarabine, is limited. Subsequent studies (Kim, et al., *Cancer Treat. Rep.,* 71:705–711, 1987) showed that the release rate of encapsulated molecules into biological fluids can be modulated by encapsulating in the presence of a hydrochloride.

Heretofore, control of the release rate of a biologically active substance from multivesicular liposomes could only be achieved by use of hydrohalides. For a drug-delivery system, it is highly advantageous to be capable of controlling the release rate for encapsulated substances through release rate modifying agents used during manufacture of the liposomes, and to have a wide choice of these release-rate modifying agents.

Accordingly, it is an object of the present invention to provide a controlled release depot preparation of multivesicular liposomes which provides a sustained exposure of a biologically active substance at a therapeutic concentration.

It is a further object of the present invention to provide a method of preparing such depot preparations.

Other and further objects, features, and advantages of the invention are inherent therein and appear throughout the specification and claims.

SUMMARY OF THE INVENTION

The compositions of the present invention comprise multivesicular liposomes (MVL), i.e. lipid vesicles with multiple internal aqueous chambers formed by non-concentric layers, and having internal membranes distributed as a network throughout the MVL, wherein the chambers contain one or more non-hydrohalic acids effective in controlling the release rate of the encapsulated biologically active substance. The present invention also provides methods of making such compositions.

The present multivesicular liposome compositions have high encapsulation efficiency, controlled release rate of the encapsulated substance, well defined, reproducible size distribution, adjustable average size that can be easily increased or decreased, and adjustable internal chamber size and number.

The process for producing these MVL compositions comprises (a) forming an emulsion from a lipid component comprising at least one organic solvent, at least one amphipathic lipid, at least one neutral lipid, and an immiscible first aqueous component comprising at least one biologically active substance and, in the presence of at least one non-hydrohalic acid, (b) mixing the emulsion with a second aqueous component to form solvent spherules, (c) removing the organic solvent from the solvent spherules to form multivesicular liposomes. According to the present invention, addition of one or more non-hydrohalic acids is effective in controlling the release rate of the encapsulated biologically active substance into biological fluids and in vivo.

DESCRIPTION OF THE DRAWING

FIG. 1 shows illustrations comparing the internal structures of a unilamellar liposome, a multilamellar liposome, and a multivesicular liposome.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The term "multivesicular liposomes" (MVL) as used throughout the specification and claims means man-made, microscopic lipid-vesicles enclosing multiple non-concentric aqueous chambers formed by internal membranes distributed as a network throughout the MVL. In contrast, unilamellar vesicles (ULV) have a single aqueous chamber; and multilamellar liposomes (MLV) have multiple "onion-skin" type of concentric membranes, in between which are concentric aqueous compartments.

The term "solvent spherule" as used throughout the specification and claims means a microscopic spheroid droplet of organic solvent, within which are suspended multiple smaller droplets of aqueous solution.

The term "neutral lipid" means oils or fats that have no membrane-forming capability by themselves and lack a hydrophilic "head" group.

The term "amphipathic lipids" means those molecules that have a hydrophilic "head" group and hydrophobic "tail" group and have membrane-forming capability

The term "zwitterionic lipid" means an amphipathic lipid with a net charge of zero at pH 7.4.

The term "anionic lipid" means an amphipathic lipid with a net negative charge at pH 7.4.

The term "cationic lipid" means an amphipathic lipid with a net positive charge at pH 7.4

The term "hydrohalic acid" means hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, or a combination thereof.

The term "biologically active substance" as used herein means a chemical compound, other than any acid used as a release-rate modifying agent according to the present invention, that is known in the art as having utility for modulating biological processes so as to achieve a desired effect in modulation or treatment of an undesired existing condition in a living being, such as a medical, agricultural or or cosmetic effect. Thus, biologically active substances are generally selected from the broad categories of medicaments, radioisotopes, agricultural products and cosmetics. Representative biologically active substances are disclosed in Table 1 below.

Briefly, the preferred method of the invention for making MVL is as follows. The first step is making a "water-in-oil" emulsion by dissolving amphipathic lipids containing at least one neutral lipid in one or more volatile organic solvents for the lipid component, adding to the lipid component an immiscible first aqueous component and a biologically active substance to be encapsulated, and adding to either or both the lipid component and the first aqueous component, a non-hydrohalic acid effective in modulating the release rate of the encapsulated biologically active substances from the MVL. The mixture is then emulsified, and then mixed with a second immiscible aqueous component to form a second emulsion. The emulsions are formed either mechanically, by ultrasonic energy, nozzle atomization, and the like, or by combinations thereof, to form solvent spherules suspended in the second aqueous component. The solvent spherules contain multiple aqueous droplets with the substance to be encapsulated dissolved in them.

The organic solvent is removed from the spherules, generally by evaporation, for instance, by reduced pressure or by passing a stream of gas over or through the suspension. When the solvent is completely removed, the spherules become MVL. Representative gases satisfactory for use in evaporating the solvent include nitrogen, helium, argon, oxygen, hydrogen, carbon dioxide, or combinations thereof.

The non-hydrohalic acid present when the MVL is formed is effective in controlling the rate of release of the encapsulated biologically active substance from the MVL into biological fluids and in vivo. The acids include, but are not limited to, perchloric acid, nitric acid, glucuronic acid, citric acid, formic acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, sulfuric acid, phosphoric acid, and combinations thereof. The amount of the acid used is that effective to provide a desired and controlled rate of release, which results in therapeutic levels of the encapsulated biologically active substance being released into a biological fluid or in vivo. For example, the concentration of the non-hydrohalic acid in the lipid component or the first aqueous component to which it is added may be in the range of 0.1 mM to about 0.5 M and preferably from about 10 mM to about 200 mM.

Many different types of volatile hydrophobic solvents such as ethers, hydrocarbons, halogenated hydrocarbons, or Freons may be used as the solvent in the lipid component. For example, diethyl ether, isopropyl and other ethers,

chloroform, tetrahydrofuran, halogenated ethers, esters, and combinations thereof are satisfactory.

Various types of lipids can be used to make the multivesicular liposomes, and the only requirements regarding lipids for making multivesicular liposomes are that at least one amphipathic lipid and one neutral lipid be included in the lipid component. The amphipathic lipids can be zwitterionic, acidic or cationic lipids. Examples of zwitterionic amphipathic lipids are phosphatidylcholines, phosphatidylethanolamines, sphingomyelins etc. Examples of acidic amphipathic lipids are phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, phosphatidic acids, etc. Examples of cationic amphipathic lipids are diacyl trimethylammonium propanes, diacyl dimethylammonium propanes, stearylamine etc. Examples of neutral lipids include diglycerides, such as diolein, dipalmitolein, and mixed caprylin-caprin; triglycerides, such as triolein, tripalmitolein, trilinolein, tricaprylin, and trilaurin; and combinations thereof Additionally, cholesterol or plant sterols can be used to make multivesicular liposomes.

Many and varied biological substances and therapeutic agents can be incorporated by encapsulation within the MVL. The drugs that can be incorporated into the dispersion system as therapeutic agents include chemicals as well as biologics. The term "chemicals" encompasses compounds that are classically referred to as drugs, such as antitumor agents, anaesthetics, analgesics, antimicrobial agents, opiates, hormones etc. Of particular interest are amikacin, morphine, hydromorphone, cytarabine, methotrexate, 5-fluorouracil (5-FU), floxuridine (FUDR), bleomycin, 6-mercapto-purine, 6-thioguanine, fludarabine phosphate, vincristine, and vinblastine.

The term "biologics" encompasses nucleic acids (DNA and RNA), proteins and peptides, and includes compounds such as cytokines, hormones (pituitary and hypophyseal hormones), growth factors, vaccines etc. Of particular interest are interleukin-2, insulin-like growth factor-1, interferons, insulin, heparin, leuprolide, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), tumor necrosis factor, inhibin, tumor growth factor alpha and beta, Mullerian inhibitory substance, calcitonin, and hepatitis B vaccine.

The following TABLE 1 includes a list of classes of biologically active substances effective in humans that can be encapsulated in MVL in the presence of a release-rate modifying non-hydrohalic acid of the invention, and also includes biologically active substances effective for agricultural uses.

TABLE 1

Antianginas	Antiarrhythmics	Antiasthmatic Agents
Antibiotics	Antidiabetics	Antifungals
Antihistamines	Antihypertensives	Antiparasitics
Antineoplastics	Antivirals	Cardiac Glycosides
Herbicides	Hormones	Immunomodulators
Monoclonal Antibodies	Neurotransmitters	Nucleic Acids
Pesticides	Proteins	Radio Contrasts
Radionuclides	Sedatives and Analgesics	Steroids
Tranquilizers	Vaccines	Vasopressors
Anesthetics	Peptides	

The term "therapeutically effective" as it pertains to the compositions of the invention means that a biologically active substance present in the first aqueous component within the vesicles is released in a manner sufficient to achieve a particular medical effect for which the therapeutic agent is intended. Examples, without limitation, of desirable medical effects that can be attained are chemotherapy, antibiotic therapy, and regulation of metabolism. Exact dosages will vary depending upon such factors as the particular therapeutic agent and desirable medical effect, as well as patient factors such as age, sex, general condition, and the like. Those of skill in the art can readily take these factors into account and use them to establish effective therapeutic concentrations without resort to undue experimentation.

Generally, however, the dosage range appropriate for human use includes the range of 0.1–6000 mg/sq m of body surface area. For some applications, such as subcutaneous administration, the dose required may be quite small, but for other applications, such as intraperitoneal administration, the dose desired to be used may be very large. While doses outside the foregoing dose range may be given, this range encompasses the breadth of use for practically all the biologically active substances.

The MVL may be administered for therapeutic applications by any desired route, for example, intramuscular, intraarticular, epidural, intrathecal, intraperitoneal, subcutaneous, intravenous, intralymphatic, oral and submucosal, and by implantation under many different kinds of epithelia, including the bronchialar epithelia, the gastrointestinal epithelia, the urogenital epithelia, and various mucous membranes of the body.

In addition, the MVL of the invention can be used to encapsulate compounds useful in agricultural applications, such as fertilizers, pesticides, and the like. For use in agriculture, the MVL can be sprayed or spread onto an area of soil where plants will grow and the agriculturally effective compound contained in the vesicles will be released at a controlled rate by contact with rain and irrigation waters. Alternatively the slow-releasing vesicles can be mixed into irrigation waters to be applied to plants and crops. One skilled in the art will be able to select an effective amount of the compound useful in agricultural applications to accomplish the particular goal desired, such as the killing of pests, the nurture of plants, etc.

The following examples illustrate the manner in which the invention can be practiced. It is understood, however, that the examples are for the purpose of illustration and the invention is not to be regarded as limited to any of the specific materials or conditions therein.

EXAMPLE 1

This example demonstrates that the release rate of a biologically active substance into an in vitro medium can be controlled by the use of different acids.

Step 1) In a clean glass cylinder (2.5 cm inner diameterx 10.0 cm height), 5 mL of a solution containing 46.5 μmoles of 1,2-dioleoyl-sn-glycero-3-phosphocholine, 10.5 μmoles of 1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol, 75 μmoles of cholesterol, 9.0 μmoles of triolein in chloroform were placed (the lipid component. The lipids were purchased from Avanti Chemical Company (Alabaster, Ala.).

Step 2) Five mL of the first aqueous component, and cytarabine (20 mg/mL) dissolved in 0.136 M of one of the acids to be tested was added into the above glass cylinder containing the lipid component. The acids tested as a release-rate modifying agent were: perchloric, nitric, formic, sulfuric, phosphoric, acetic, trichloroacetic, and trifluoroacetic acids.

Step 3) For making the water-in-oil emulsion, a homogenizer (AutoHomoMixer, Model M, Tokushu Kika, Osaka, Japan) was used by mixing for 8 minutes at a speed of 9000 rpm.

Step 4) For making the chloroform spherules suspended in water, 20 mL of a solution containing 4 wt % glucose and 40 mM lysine was layered on top of the water-in-oil emulsion, and then mixed for 60 seconds at a speed of 4000 rpm to form the chloroform spherules.

Step 5) The chloroform spherule suspension in the glass cylinder was poured into the bottom of a 1000 mL Erlenmeyer flask containing 30 mL of water, glucose (3.5 g/100 mL), and free-base lysine (40 mM). A stream of nitrogen gas was passed at a flow-rate of 7 L/minute over the suspension in the flask to evaporate chloroform over 20 minutes at 37° C. Sixty mL of normal saline (0.9% sodium chloride) was added to the flask. The MVL were then isolated by centrifugation at 600 X g for 10 minutes. The supernatant was decanted, and the pellet was resuspended in 50 mL of normal saline. The pellet was resuspended in saline to yield a final concentration of 10 mg cytarabine per mL of suspension.

A laser diffraction particle size analyzer (Horiba Instruments, Irvine, Calif.) was used to determine particle size. The average length-weighted mean diameter of the resulting MVL particles was in the range from 12–16 μm.

The use of different non-hydrohalic acids as release-modifying agents had marked influence on the rate of cytarabine release from the MVL incubated in human plasma. The percent of cytarabine retained in the MVL after incubation at 37° C. in human plasma for the different acids is measured as a function of time of incubation. The half-life of drug release, calculated assuming a single-exponential, is given in TABLE 2. The data in TABLE 2 are the mean and standard deviation from three experiments.

TABLE 2

Acid	Half Life in Days for Release of Cytarabine
Perchloric Acid	37.2 ± 8.0
Nitric Acid	54.5 ± 5.7
Phosphoric Acid	6.5 ± 0.2
Formic Acid	5.6 ± 0.2
Trichloroacetic Acid	5.5 ± 0.6
Acetic Acid	4.8 ± 0.5
Trifluoroacetic Acid	3.4 ± 0.4
Sulfuric Acid	1.6 ± 0.5

The nature of the release-rate modifying non-hydrohalic acid used to prepare the multivesicular liposomes had a profound effect on the release rates of cytarabine in human plasma. Use of monoprotic inorganic acids, namely, nitric acid, and perchloric acid, resulted in the slowest release rate for cytarabine. Diprotic and triprotic acids, i.e., sulfuric acid and phosphoric acid, resulted in fast release rates. The organic acids, formic acid, acetic acid, trifluoroacetic acid and trichloroacetic acid, also resulted in fast release rates. Thus, a desired release rate can be achieved by selecting an appropriate acid as illustrated herein.

EXAMPLE 2

This example demonstrates that the rate of release of leuprolide from MVL into an in vitro medium can be controlled by varying the acid.

Step 1) In a clean conical Teflon tube, 2 mL of a solution containing 78.88 μmoles of 1,2-dioleoyl-sn-glycero-3-phosphocholine, 16.65 μmoles of 1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol, 118.8 μmoles of cholesterol, 14.6 μmoles of triolein in chloroform were placed (the lipid component). The lipids were purchased from Avanti Chemical Company (Alabaster, Ala.).

Step 2) Two mL of first aqueous component, leuprolide (10 mg/nL) dissolved 0.1 M phosphoric acid, or ascorbic acid, or 0.2 M citric acid, or glucuronic acid, were added into the above Teflon tube containing lipid component.

Step 3) For making the water-in-oil emulsion, a homogenizer (AutoHomoMixer, Model M, Tokushu Kika, Osaka, Japan) was used by mixing for 7 minutes at a speed of 10,000 rpm.

Step 4) For making the chloroform spherules suspended in water, 20 mL of a solution containing 4 wt % glucose and 40 mM lysine was added to the water-in-oil emulsion, and then mixed for 2 minutes at a speed of 2000 rpm to form the chloroform spherules.

Step 5) The chloroform spherule suspension in the glass cylinder was poured into the bottom of a 1000 mL Erlenmeyer flask containing 30 mL of water, 4 wt % glucose, and 40 mM free-base lysine. A stream of nitrogen gas was passed at a flow-rate of 50 cu ft/hr over the suspension in the flask to evaporate chloroform over 20 minutes at 37° C. The MVL were then isolated by centrifugation at 600 X g for 10 minutes.

The half life values in days for the plasma release were 15.8±8.4, 4.7±1.5, 6.0±1.5, and 3.0±0.2, for phosphoric acid, ascorbic acid, citric acid, and glucuronic acid, respectively.

EXAMPLE 3

This example demonstrates that a mixture of zwitterionic amphipathic lipids and a neutral lipid can be used for producing the MVL compositions with an acid used in the process.

The procedure for the preparation of MVL was the same as in EXAMPLE 1, with the following exceptions.

For Step 1, into a clean glass cylinder (2.5 cm inner diameter×10.0 cm height) were placed 5 mL of a solution containing 13.20 μmoles of 1,2-dioleoyl-sn-glycero-3-phosphocholine, 2.79 μmoles of 1,2-dipalmitoyl-sn-glycerol-3-phosphoethanolamine, 19.88 μmoles of cholesterol, and 2.48 μmoles of triolein in chloroform (the lipid component).

In Step 2, 5 mL of the first aqueous component and cytarabine (20 mg/mL) dissolved in 0.136 M sulfuric acid were added into the above glass cylinder containing the lipid component.

The half life value for in vitro release was 3.0±1.6 days.

EXAMPLE 4

This is an example for the antibacterial agent, amikacin, encapsulated into MVL in the presence of an non-hydrohalic acid.

The procedure for the preparation of MVL was the same as in EXAMPLE 1, with the following exceptions.

For Step 1, into a clean glass cylinder (2.5 cm inner diameter×10.0 cm height) were placed 5 mL of a solution containing 13.20 μmoles of 1,2-dioleoyl-sn-glycero-3-phosphocholine, 2.79 μmoles of 1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol, 19.88 μmoles of cholesterol, 2.48 μmoles of triolein in chloroform (the lipid component).

In Step 2, 5 mL of the first aqueous component and amikacin (20 mg/mL) dissolved in 0.136 M sulfuric acid were added into the above glass cylinder containing the lipid component.

The half life value in plasma was 16.6±2.1 days.

Thus, the present disclosure provides "depot" preparations of wide application and uses in which biologically active substances are encapsulated in relatively large

amounts, provide sustained exposure or delivery at therapeutic concentrations of these substances for optimal results, and the release rate of the substance is controlled by varying the nature of the acid used in the formulation.

For a given biologically active substance, one skilled in the art will be able to choose an acid to produce an MVL composition with a desired release rate of the encapsulated biologically active substance.

The present invention, therefore, is well suited and adapted to attain the ends and objects and has the advantages and features mentioned as well as others inherent therein.

While presently preferred embodiments of the invention have been given for the purpose of disclosure, it should be understood that various modifications can be made without departing from the spirit and scope of the invention. Accordingly, the following claims are intended to be interpreted to embrace all such modifications.

What is claimed is:

1. A multivesicular liposome having multiple non-concentric chambers with internal membranes distributed as a network throughout, produced by a method comprising the steps of:

(a) forming a water-in-oil emulsion from two immiscible components, the two immiscible components being:

1) a lipid component comprising at least one organic solvent, at least one amphipathic lipid, and at least one neutral lipid lacking a hydrophilic head group, and

2) a first aqueous component;

said water-in-oil emulsion further comprising:

3) non-hydrohalic acid in a concentration range from about 0.1 mM to about 0.5 M, wherein the concentration is selected to provide controlled release of the biologically active substance in 4) from the liposome, and

4) at least one biologically active substance;

said non-hydrohalic acid and said biologically active substance being independently incorporated into the lipid component, the first aqueous component, or both;

(b) mixing the water-in-oil emulsion containing the non-hydrohalic acid with a second aqueous component to form solvent spherules; and thereafter

(c) removing the organic solvent from the solvent spherules to form multivesicular liposomes.

2. The liposome of claim 1, wherein the acid is selected from the group consisting of sulfuric acid, phosphoric acid, and acetic acid, and combinations thereof and wherein the controlled release is at physiologic conditions.

3. The liposome of claim 1, wherein the acid is selected from the group consisting of nitric, formic, sulfuric, phosphoric, acetic, glucuronic, citric, and combinations thereof.

4. The liposome of claim 1, wherein the biologically active agent is selected from the group consisting of an antitumor agent, an anaesthetic, an analgesic, an antimicrobial agent, a hormone, an antiasthmatic agent, a cardiac glycoside, an antihypertensive, a vaccine, an antiarrhythmic, an immunomodulator, a steroid, a monoclonal antibody, a neurotransmitter, a radionuclide, a radio contrast agent, a nucleic acid, a protein, a herbicide, a pesticide, and suitable combinations thereof.

5. The liposome of claim 1, wherein the biologically active substance is cytarabine.

6. The liposome of claim 1, wherein the biologically active substance is amikacin.

7. The liposome of claim 1, wherein the biologically active substance is hydromorphone.

8. The liposome of claim 1, wherein the biologically active substance is leuprolide.

9. The liposome of claim 1, wherein the biologically active substance is insulin.

10. The liposome of claim 1, wherein the biologically active substance is interleukin-2.

11. The liposome of claim 1, wherein the biologically active substance is insulin-like growth factor-1.

12. The liposome of claim 1, wherein the biologically active substance is an interferon.

13. The liposome of claim 1, wherein the biologically active substance is granulocyte colony stimulating factor (G-CSF).

14. The liposome of claim 1, wherein the biologically active substance is tumor necrosis factor.

15. The liposome of claim 1, wherein the biologically active substance is tumor growth factor alpha.

16. The liposome of claim 1, wherein the biologically active substance is tumor growth factor beta.

17. The liposome of claim 1, wherein the biologically active substance is morphine.

18. The liposome of claim 1, wherein the controlled release of the biologically active substance is sufficient to ameliorate a disease following administration of the liposome to a living mammal.

19. The liposome of claim 1, wherein the biologically active substance is selected from the group consisting of herbicides and pesticides.

20. The liposome of claim 1, wherein the amphipathic lipid is provided in admixture with cholesterol, plant sterols, or combinations thereof.

21. The liposome of claim 1, wherein the amphipathic lipid is a zwitterionic lipid.

22. The liposome of claim 1, wherein the amphipathic lipid is an anionic lipid.

23. The liposome of claim 1, wherein the amphipathic lipid is a mixture of a zwitterionic lipid and an anionic lipid.

24. The liposome of claim 1, wherein the amphipathic lipid is a mixture of a zwitterionic lipid and a cationic lipid.

25. The liposome of claims 1, 20, 22, and 23, wherein the zwitterionic lipid is selected from the group consisting of phosphatidylcholines, phosphatidylethanolamines, sphingomyelins, lysophosphatidylcholines, lysophosphatidylethanolamines, and combinations thereof.

26. The liposome of claims 1, 21, and 22, wherein the anionic lipid is selected from the group consisting of phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, phosphatidicacids, cardiolipins, and combinations thereof.

27. The liposome of claims 1 and 23, wherein the cationic lipid is selected from the group consisting of diacyl trimethylammonium propanes, diacyl dimethylammonium propanes, stearylamine, and combinations thereof.

28. The liposome of claim 1, wherein the neutral lipid is selected from the group consisting of triglycerides, diglycerides, ethylene glycols, and combinations thereof.

29. The liposome of claim 1, wherein the organic solvent is selected from the group consisting of ethers, hydrocarbons, halogenated hydrocarbons, halogenated ethers, esters, and combinations thereof.

30. The liposome of claim 1, wherein the emulsification of the two immiscible components is carried out using a method selected from the group consisting of mechanical agitation, ultrasonic energy agitation, and nozzle atomization.

31. The liposome of claim 1, wherein the formation of the solvent spherules is carried out using a method selected from

the group consisting of mechanical agitation, ultrasonic energy agitation, and nozzle atomization.

32. The liposome of claim 1, wherein the removal of the organic solvent is by a method selected from the group consisting of sparging, rotary evaporation, passing gas over the solvent spherule suspension, solvent selective filtration, and combinations thereof.

33. The liposome of claim 1, wherein the concentration of the organic solvent is in the range from about 3.98 mM to about 15 mM, the concentration of the amphipathic lipid is in the range from about 3.2 mM to about 47.77 mM, and the concentration of the neutral lipid is in the range from about 0.5 mM to about 7.3 mM.

34. The liposome of claim 33, wherein the amphipathic lipid is a combination of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) in a concentration from about 2.64 mM to about 39.44 mM and 1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol (DPPG) in a concentration from about 0.56 to about 8.33 mM.

35. The liposome of claim 1, wherein the non-hydrohalic acid is selected from the group consisting of nitric acid, glucuronic acid, citric acid, formic acid, acetic acid, sulfuric acid, phosphoric acid, and combinations thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,132,766 Page 1 of 2
DATED : OCTOBER 17, 2000
INVENTOR(S) : SANKARAM BHIMA MANTRIPRAGADA, PH.D. ET AL.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Page 2, Col. 2: Kim, [Kim, Kim,] Cancer Chemother. Pharmacol., 33:187-190, 1993, "Extended-release formulation of morphine for subcutaneous administration".

Col. 5, Lines 57-58 (Table 1) reformatted:

TABLE 1

Antianginas	Antiarrhythmics	Antiasthmatic Agents
Antibiotics	Antidiabetics	Antifungals
Antihistamines	Antihypertensives	Antiparasitics
Antineoplastics	Antivirals	Cardiac Glycosides
Herbicides	Hormones	Immunomodulators
Monoclonal Antibodies	Neurotransmitters	Nucleic Acids
Pesticides	Proteins	Radio Contrasts
Radionuclides	Sedatives and Analgesics	Steroids
Tranquilizers	Vaccines	Vasopressors
Anesthetics	Peptides	

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,132,766

DATED : OCTOBER 17, 2000

INVENTOR(S) : SANKARAM BHIMA MANTRIPRAGADA, PH.D. ET AL.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 6, Line 55: (the lipid component).

Col. 7, Line 67: "10 mg/[nL]mL

Signed and Sealed this

Fifteenth Day of May, 2001

Attest:

Nicholas P. Godici

NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office

EXHIBIT F

Attorney's Docket No.: 07333-022002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Mantripragada B. Sankaram et al. Art Unit : 1648
Serial No. : 09/045,236 Examiner : Padmashri Ponnaluri
Filed . : March 20, 1998
Title : **MULTIVESICULAR LIPOSOMES WITH CONTROLLED RELEASE OF ENCAPSULATED BIOLOGICALLY ACTIVE SUBSTANCES**

Assistant Commissioner for Patents
Washington, D.C. 20231

TERMINAL DISCLAIMER UNDER 37 CFR §§3.73(b) AND 1.321(b)

Pursuant to 37 CFR §3.73(b), SKYEPHARMA INC., a corporation, certifies that it is the assignee of the entire right, title, and interest in the above application by virtue of:

☒ An assignment from the inventors of the patent application identified above. The assignment was recorded in the Patent and Trademark Office for the parent application at Reel 7762, Frame 0186 on September 11, 1995 and for the subject application at Reel 010121, Frame 0893 on August 2, 1999.

The undersigned has reviewed all the documents in the chain of title of the above-identified application and to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee.

Pursuant to 37 CFR §1.321(b), and to obviate a double patenting rejection, the assignee identified above hereby waives and disclaims the terminal portion of the term of the entire patent to be granted upon the above identified application subsequent to the expiration date of U.S. Patent No. 5,807,572. Further, any patent granted on the above identified application shall be

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

December 16, 1999
Date of Deposit

Anthony D. Hyde
Signature

Anthony D. Hyde
Typed or Printed Name of Person Signing Certificate

12/27/1999 MSHIFERA 00000011 09045236
02 FC:248 55.00 OP

enforceable only for and during such period that said patent is commonly owned with U.S. Patent No. 5,807,572.

The assignee identified above does not disclaim any terminal part of any patent granted on the above identified application prior to the expiration date of the full statutory term of U.S. Patent No. 5,807,572 in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR §1.321, has all claims cancelled by a reexamination certificate, or is otherwise terminated prior to expiration of its statutory term, except for the separation of legal title as stated above.

This disclaimer runs with any patent granted on the above application and is binding upon the grantee, its successors or assigns.

Enclosed is a check for $55 for the required fee pursuant to 37 CFR §1.20(d).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 12-15-99

Diane L. Gardner
Registration No. 36,518

Attorney for Applicant

DLG/int2

Fish & Richardson P.C.
4225 Executive Square, Suite 1400
La Jolla, CA 92037
Telephone: (858) 678-5070
Facsimile: (858) 678-5099

10005679.doc

Attorney's Docket No.: 07333-022002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Mantripragada B. Sankaram et al. Art Unit : 1648
Serial No. : 09/045,236 Examiner : Padmashri Ponnaluri
Filed : March 20, 1998
Title : **MULTIVESICULAR LIPOSOMES WITH CONTROLLED RELEASE OF ENCAPSULATED BIOLOGICALLY ACTIVE SUBSTANCES**

Assistant Commissioner for Patents
Washington, D.C. 20231

TERMINAL DISCLAIMER UNDER 37 CFR §§3.73(b) AND 1.321(b)

Pursuant to 37 CFR §3.73(b), SKYEPHARMA INC., a corporation, certifies that it is the assignee of the entire right, title, and interest in the above application by virtue of:

☒ An assignment from the inventors of the patent application identified above. The assignment was recorded in the Patent and Trademark Office for the parent application at Reel 7762, Frame 0186 on September 11, 1995 and for the subject application at Reel 010121, Frame 0893 on August 2, 1999.

The undersigned has reviewed all the documents in the chain of title of the above-identified application and to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee.

Pursuant to 37 CFR §1.321(b), and to obviate a double patenting rejection, the assignee identified above hereby waives and disclaims the terminal portion of the term of the entire patent to be granted upon the above identified application subsequent to the expiration date of U.S.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

December 16, 1999
Date of Deposit

Signature

Anthony D. Hyde
Typed or Printed Name of Person Signing Certificate

12/27/1999 MSHIFERA 00000011 09045236
04 FC:248 55.00 OP

Serial No. 08/305,158 now allowed. Further, any patent granted on the above identified application shall be enforceable only for and during such period that said patent is commonly owned with U.S. Serial No. 08/305,158.

The assignee identified above does not disclaim any terminal part of any patent granted on the above identified application prior to the expiration date of the full statutory term of U.S. Serial No. 08/305,158 in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR §1.321, has all claims cancelled by a reexamination certificate, or is otherwise terminated prior to expiration of its statutory term, except for the separation of legal title as stated above.

This disclaimer runs with any patent granted on the above application and is binding upon the grantee, its successors or assigns.

Enclosed is a check for $55 for the required fee pursuant to 37 CFR §1.20(d).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 12·15·99

Diane L. Gardner
Registration No. 36,518

Attorney for Applicant

DLG/int2

Fish & Richardson P.C.
4225 Executive Square, Suite 1400
La Jolla, CA 92037
Telephone: (858) 678-5070
Facsimile: (858) 678-5099

10005679.doc

EXHIBIT G

Attorney Docket No.: 07333-022002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Mantripragada B. Sankaram et al.	Art Unit	: 1648
Patent No.	: 6,132,766	Examiner	: Padmashri Ponnaluri
Issue Date	: October 17, 2000	Batch No.	: H62
Serial No.	: 09/045,236		
Filed	: March 20, 1998		
Title	: MULTIVESICULAR LIPOSOMES WITH CONTROLLED RELEASE OF ENCAPSULATED BIOLOGICALLY ACTIVE SUBSTANCES		

#17
JW

Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF REQUEST FOR CERTIFICATE OF CORRECTION

Applicant hereby requests that a certificate of correction be issued for the above patent in accordance with the attached request.

All errors sought to be corrected were made in printing by the Patent and Trademark Office and no fee is believed to be due.

Please apply any charges or credits to Deposit Account No. 06-1050.

CERTIFICATE
JAN 8 2001
OF CORRECTION

Respectfully submitted,

Date: 10/5/00

Diane L. Gardner
Reg. No. 36,518

Fish & Richardson P.C.
4350 La Jolla Village Drive, Suite 500
San Diego, CA 92122
Telephone: (858) 678-5070
Facsimile: (858) 678-5099

10068845.doc

APPROVED
MAR 2 1 2001 LW
FOR THE DIRECTOR OF USPTO

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

December 5, 2000
Date of Deposit

Signature

Anthony D. Hyde
Typed or Printed Name of Person Signing Certificate

PUBLISH

Staple Here Only

Printer's Trim Line →

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,132,766

DATED : OCTOBER 17, 2000

INVENTOR(S) : SANKARAM BHIMA MANTRIPRAGADA, PH.D. ET AL.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Page 2, Col. 2: Kim, [Kim, Kim,] Cancer Chemother. Pharmacol., 33:187-190, 1993, "Extended-release formulation of morphine for subcutaneous administration".

Col. 5, Lines 57-58 (Table 1) reformatted:

TABLE 1

Antianginas	Antiarrhythmics	Antiasthmatic Agents
Antibiotics	Antidiabetics	Antifungals
Antihistamines	Antihypertensives	Antiparasitics
Antineoplastics	Antivirals	Cardiac Glycosides
Herbicides	Hormones	Immunomodulators
Monoclonal Antibodies	Neurotransmitters	Nucleic Acids
Pesticides	Proteins	Radio Contrasts
Radionuclides	Sedatives and Analgesics	Steroids
Tranquilizers	Vaccines	Vasopressors
Anesthetics	Peptides	

Col. 6, Line 55: (the lipid component).

Col. 7, Line 67: "10 mg/[nL]mL

MAILING ADDRESS OF SENDER:

Diane L. Gardner
Fish & Richardson P.C.
4350 La Jolla Village Drive, Suite 500
San Diego, CA 92122

PATENT NO. 6,132,766

No. of add'l copies @ 50¢ per page 0

SUBSTITUTE FORM PTO 1050

Staple Here Only

Printer's Trim Line →

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,193,998 B1

DATED : FEBRUARY 27, 2001

INVENTOR(S) : QIANG YE AND MANTRIPRAGADA BHIMA SANDARAM

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 9, line 20, please delete "37° C." and insert --37°C-- therefore.

In column 16, line 52, please delete "clam" and insert --claim-- therefore.

In column 16, line 64, please delete "sn" and insert --*sn*-- therefore.

In column 16, line 65, please delete "sn" and insert --*sn*-- therefore.

In column 16, line 66, please delete "sn" and insert --*sn*-- therefore.

In column 16, line 67, please delete "sn" and insert --*sn*-- therefore.

In column 17, line 1, please delete "sn" and insert --*sn*-- therefore.

In column 17, line 2, please delete "sn" and insert --*sn*-- therefore.

In column 17, line 3, please delete "sn" and insert --*sn*-- therefore.

In column 17, line 4, please delete "sn" and insert --*sn*-- therefore.

In column 17, line 5, please delete "sn" and insert --*sn*-- therefore.

In column 17, line 6, please delete "sn" and insert --*sn*-- therefore.

In column 17, line 7, please delete "sn" and insert --*sn*-- therefore.

MAILING ADDRESS OF SENDER:

Diane L. Gardner
Fish & Richardson P.C., P.A.
4350 La Jolla Village Drive
Suite 500
San Diego, CA 92122

PATENT NO. 6,193,998 B1

No. of add'l copies @ 50¢ per page number

SUBSTITUTE FORM PTO 1050

Staple Here Only

Printer's Trim Line →

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,193,998 B1

DATED : FEBRUARY 27, 2001

INVENTOR(S) : QIANG YE AND MANTRIPRAGADA BHIMA SANDARAM

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 17, line 8, please delete "sn" and insert --*sn*-- therefore.

MAILING ADDRESS OF SENDER:

Diane L. Gardner
Fish & Richardson P.C., P.A.
4350 La Jolla Village Drive
Suite 500
San Diego, CA 92122

PATENT NO. 6,193,998 B1

No. of add'l copies @ 50¢ per page number

SUBSTITUTE FORM PTO 1050

EXHIBIT H

Maintenance Report

Patent Bibliographic Data					12/14/2011 05:49 PM
Patent Number:	6132766		Application Number:	09045236	
Issue Date:	10/17/2000		Filing Date:	03/20/1998	
Title:	MULTIVESICULAR LIPOSOMES WITH CONTROLLED RELEASE OF ENCAPSULATED BIOLO				
Status:	12th year fee window opens: 10/17/2011			Entity:	Small
Window Opens:	10/17/2011	Surcharge Date:	04/18/2012	Expiration:	N/A
Fee Amt Due:	$2,365.00	Surchg Amt Due:	$0.00	Total Amt Due:	$2,365.00
Fee Code:	2553	MAINTENANCE FEE DUE AT 11.5 YEARS			
Surcharge Fee Code:					
Most recent events (up to 7):	04/15/2008 03/26/2008 03/26/2008 05/07/2004 05/07/2004 05/05/2004	Payment of Maintenance Fee, 8th Yr, Small Entity. Payor Number Assigned. Payer Number De-assigned. Payment of Maintenance Fee, 4th Yr, Small Entity. Surcharge for late Payment, Small Entity. Maintenance Fee Reminder Mailed. --- End of Maintenance History ---			
Address for fee purposes:	KNOBBE MARTENS OLSON & BEAR LLP 2040 MAIN STREET FOURTEENTH FLOOR IRVINE CA 92614				

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 20995 | ISTMT | DATE PRINTED 04/15/2008

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE CA 92614

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,132,766	**$1,180.00**	**$0.00**	**04/15/08**	**09/045,236**	**10/17/00**	**03/20/98**	**08**	**YES**	**PCIRA.5CPCDV1**

EXHIBIT I

File Information						
CUSTOMER NAME: Pacira Pharmaceuticals, Inc. DATE: 10/25/11 TIME: 9:40 am PREPARED BY: Anna Franco				DAR NO.	DATE	F
C.E.N. NUMBER	PART NUMBER	C.A.D.	PRESS	OK TO MAKE FILES	DATE	
013039–01	TBD	PACIRA 002	Post HH			
BLACK PANTONE 2627 C PANTONE 3145 C				OUTLINE	APPLICATION Illustrator CS4	

PROOF & (COPYRIGHT) APPROVAL

This proof of your artwork shows type style, size and location. Check all data carefully for accuracy.
Upon receipt of your approval, your order will be printed EXACTLY according to this proof.
Approval signifies that the signed proof supersedes any documentation supplied with the order. In the event differences exist.
Materials and ink colors will be in accordance with your order. Any colors shown on the proof may not be representative of actual PMS colors.
No credit will be given for printed product whose copy conforms to this proof.

APPROVED ☐ SIGNATURE/DATE | APPROVED with changes ☐ SIGNATURE/DATE | MAKE CHANGES and send another proof ☐ SIGNATURE/DATE

Royal Paper Box Company • 1185 S. Maple Ave Montebello CA. 90640

EXPAREL
bupivacaine liposome injectable suspension
1.3%
266 mg/20mL (13.3 mg/mL)
For infiltration ONLY. Not for any other route of administration.

Storage: Protect from freezing, Refrigerate 2°C to 8°C (36°F to 46°F). Do not filter. Product can be stored at controlled room temperatures not exceeding 25°C (77°F) for up to 30 days prior to use. Store vials in outer carton.

Single use vial; discard any unused portion.

See package insert for additional storage information.

Manufactured by: PACIRA San Diego, CA 92121 10450 Science Center Drive

LOT

EXP

NDC 65250-266-20

EXPAREL
bupivacaine liposome injectable suspension
1.3%
266 mg/20mL (13.3 mg/mL)
For infiltration ONLY. Not for any other route of administration.

Storage: Protect from freezing.

EXPAREL
bupivacaine liposome injectable suspension
1.3%
266 mg/20mL (13.3 mg/mL)
For infiltration ONLY. Not for any other route of administration.

Part No.: XXXXXXX

NO COAT

NDC 65250-266-20

EXPAREL
bupivacaine liposome injectable suspension
1.3%
266 mg/20mL (13.3 mg/mL)
For infiltration ONLY. Not for any other route of administration.

Contents: Each 20 mL vial contains 266 mg of bupivacaine free base.
Usual Dosage: See package insert. Do not substitute for or with other formulations containing bupivacaine or bupivacaine HCl.
10 Vials per Carton

Rx Only

EXPAREL
bupivacaine liposome injectable suspension
1.3%
266 mg/20mL (13.3 mg/mL)
For infiltration ONLY. Not for any other route of administration.

Part No.: XXXXXXX

NO COAT

EXHIBIT J

SkyePharma

December 9, 2004

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care and
Addictive Drug Products (HFD-170)
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

Attention: Central Document Room

Subject: SKY0402 (bupivacaine extended-release liposome injection)
Other Names: sustained-release encapsulated bupivacaine; DepoBupivacaine
Initial IND (Pre-IND 69,198)

Dear Dr. Rappaport,

SkyePharma Inc. is hereby submitting, in triplicate, the initial IND for SKY0402 (bupivacaine extended-release liposome injection) in CTD format using the draft Table of Contents, "Comprehensive Table of Contents Heading and Hierarchy," provided by the Division on 5 November 2004. The IND includes two proposed Phase 2 clinical protocols:

> *Protocol Number SKY0402-C-201, "A Phase 2, Multicenter, Randomized, Double-Blind, Dose-Escalating/De-Escalating Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of a Single Dose of Sustained-Release Encapsulated Bupivacaine (SKY0402) in the Management of Post-Operative Pain in Subjects Undergoing Inguinal Hernia Repair"*
>
> *Protocol Number SKY0402-C-203, "A Phase 2, Multicenter, Randomized, Double-Blind, Dose-Escalating/De-Escalating Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Sustained-Release Encapsulated Bupivacaine (SKY0402) Administered as a Nerve Block in the Management of Post-Operative Pain in Subjects Undergoing Bunionectomy"*

SkyePharma met with the Division on 2 October 2002 for a Pre-IND meeting. The Division provided an agenda at the meeting (a copy is included in Volume 1, Module 1, Section 1.12.1). The Division also had a teleconference with SkyePharma on 19 December 2002 to discuss the revised development plans for SKY0402 in response to the Pre-IND meeting. A Pre-Investigational New Drug Application (PIND) file was opened

for SKY0402, PIND #69,198, in June/July 2004. The current nonclinical and clinical plans have changed since these meetings and an updated General Investigational Plan is provided in Module 1, Section 1.13.9.

All of the CMC information for SKY0402 is provided in Module 2, Section 2.3, Quality Overall Summary, therefore Module 3 has been omitted from this initial IND.

If you need additional information or have any questions, please contact me by phone at (858) 625-2414 ext. 3370, by facsimile 858-623-0376 or by email gordon_schooley@skyepharma.com.

Regards,

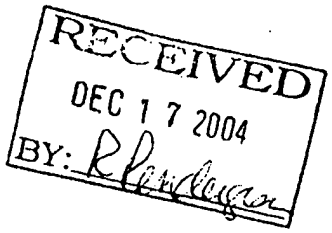
Gordon L. Schooley, Ph.D.
Chief Scientific Officer

97109

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857



IND 69, 198

SkyePharma, Inc.
10450 Science Center Drive
San Diego, CA 92121

Attention: Gordon L. Schooley, Ph.D.
Chief Scientific Officer

Dear Dr. Schooley:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	69, 198
Sponsor:	SkyePharma, Inc.
Name of Drug:	SKY0402 (sustained-release encapsulated bupivacaine)
Date of Submission:	December 9, 2004
Date of Receipt:	December 10, 2004

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before January 9, 2005, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic Critical Care and
Addiction Drug Products (HFD-170)
Attention: Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions call me at (301) 827-7432.

Sincerely yours,

{See appended electronic signature page}

Kimberly Compton, R. Ph.
Regulatory Project Manager
Division of Anesthetic Critical Care and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kimberly Compton
12/10/04 06:13:41 PM

From: "Compton, Kimberly" <ComptonK@cder.fda.gov>
To: "'Paula Adams'" <Paula_Adams@skyepharma.com>
Date: 1/5/2005 10:58:28 AM
Subject: F-U to VM msg just left

"MMS <skyepharma.com>" made the following annotations.

This secure message was sent using an SPN
==========

Hi Paula,

I understand Gordon in on travel, so I hope you can help me. I left you a VM saying this same thing just now, but am leaving to work at home rest of the day so email will be best way to f-u this afternoon so wanted to make sure you had my email and that the attached memo I emailed to Gordon yesterday got opened so a response could be drafted.

1. A copy of the memo is attached.
2. We need to set up a TC for tomorrow (Thur, 1/6/05) to discuss issues with the IND. Our Clinical and PreClinical team will be the main ones involved, but our CMC and PK folks might attend (but I don't think so). Also, our Deputy Div Dir will be there. The main problem is that on such short notice our calendar is very full and I am wondering if 11 am EST (8 for you) will work? If it absolutely will not, I will try to find another slot by moving some things if I can, but hope this works.

Thanks for your help and look forward to hearing from you this afternoon.

Thanks,
Kim Compton
301-827-7432 (office)

CC: "Compton, Kimberly" <ComptonK@cder.fda.gov>

Memo of Needed Information - Communicated to Sponsor by email

Date: 1-04-05 (Clinical Request #2)

From: Kim Compton, Regulatory Project Manager, HFD-170/CDER/FDA
(Comptonk@cder.fda.gov, fax # 301-443-7068, phone 301-827-7432)

To: Gordon L. Schooley, Ph.D., Chief Scientific Officer, SkyePharma, Inc.
(Gordon_Schooley@skyepharma.com, fax # 858-623-0376, phone 858-625-2414 ext. 3370)

Re: IND 69, 198 - SKY0402 (bupivacaine extended-release liposome injection)

The Agency requires responses to the items listed below to completely review your new IND submission. Please provide a response ***as soon as possible.***

> ****Please note:*** As with all initial IND reviews, we require **complete information** so that we may make a determination of whether the IND is "safe-to-proceed" or not. Without complete information, it could become necessary to place your IND on Clinical Hold until all information is received for our review. Therefore we request that you make every effort to submit the requested information to allow time for our review prior to your "30-day Safety Date" (the point at which we must make a determination for "safe-to-proceed" or not.) That date for this IND is Friday, January 7, 2004.

You may respond by email, fax or both, as is your preference, always following with a "hard copy" (exact duplicate) submission to the IND file. My contact information is listed above should you have any questions or concerns.

1. In the submitted form 1571 you indicated that no part of the clinical study would be conducted by a contract research organization (CRO), yet in your response to question #2 from our first set of Clinical requests, regarding who will actually review the data before the patient is moved to the next cohort, you indicated that a CRO (i3 StatProbe) will be responsible for data management. Please clarify who is responsible for what aspects of conducting your study.

2. The studies are described several times as "dose escalation/de-escalation", and it is noted that an internal data evaluation committee will decide whether to increase or decrease the bupivacaine dose, yet there is no schema for dose reduction. A table is provided for dose escalation along with a formula for decision-making with regard to drug concentration. How does dose *de-escalation* proceed?

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kimberly Compton
1/4/05 03:19:13 PM
CSO

EXHIBIT K

SkyePharma

January 6, 2005

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and
Addictive Drug Products (HFD-170)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attention: Document Control Room #8B-45

Subject: Investigational New Drug (IND) 69,198
SKY0402 (bupivacaine extended-release liposome injection)
Serial No. 005
Inactivation of IND 69,198

Dear Dr. Rappaport,

SkyePharma Inc. hereby inactivates IND 69,198 for SKY0402 (bupivacaine extended-release liposome injection). Reference is made to the original IND submission dated December 9, 2004. Investigational drug has not been shipped to US clinical sites.

If you have any questions regarding this submission, please contact me by telephone at (858) 625-2414, 3370, by facsimile 858-623-0376 or by email at gordon_schooley@skyepharma.com.

Sincerely,

Gordon L. Schooley, PhD
Chief Scientific Officer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
SkyePharma Inc.

2. DATE OF SUBMISSION
January 6, 2005

3. ADDRESS *(Number, Street, City, State and Zip Code)*
10450 Science Center Drive
San Diego, CA 92121

4. TELEPHONE NUMBER *(Include Area Code)*
(858) 625-2424

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
SKY0402 (Bupivacaine extended-release liposome injection)
Other: sustained-release encapsulated bupivacaine, DepoBupivacaine

6. IND NUMBER *(If previously assigned)*
69,198

7. INDICATION(S) *(Covered by this submission)*
Post-operative pain management

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☒ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.
US DMF Number 11938, 14604, 16080, 12185, 3872

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
0 0 0 5

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☒ OTHER Inactivation of IND 69,198 *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☒ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Gordon L. Schooley, PhD
Chief Scientific Officer
SkyePharma Inc.

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Garen Manvelian, MD, Medical Director
Medical Monitor
SkyePharma Inc.

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Gordon L. Schooley, PhD Chief Scientific Officer SkyePharma Inc.	for	
18. ADDRESS *(Number, Street, City, State and Zip Code)* 10450 Science Center Drive San Diego, CA 92121	19. TELEPHONE NUMBER *(Include Area Code)* (858) 625-2424	20. DATE 1/6/05

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

FORM FDA 1571, Box 13

The Transfer of Obligations to a Contract Research Organization (21 CFR 312.52)

As set forth in 21 CFR 312.52, the following obligations for the conduct of clinical studies SKY0402-C-201 and SKY0402-C-203 have been transferred to the listed CROs.

CRO	Obligations Transferred
i3 Statprobe Ann Arbor, MI Office 5430 Data Court , Suite 200 Ann Arbor, MI 48108 Phone: 734.769.5000; Fax: 734.769.5344 San Diego, CA Office 10052 Mesa Ridge Court, Suite 200 San Diego, CA 92121 Phone: 858.597.1000; Fax: 858.597.1004	Global data management and statistical analysis
Novotech (Australia) Pty Ltd Level 3, 19 Harris Street Pyrmont, NSW 2009 Tel: +61 (0)2 9518 9600 Fax: +61 (0)2 9518 9390	Clinical monitoring and local project management support in Australia
INC Research Global Headquarters Raleigh, North Carolina 4700 Falls of Neuse Road Suite 400 Raleigh, NC 27609 Fax: 919.876.9360 Toll-Free: 866.462.7373 United Kingdom (London) 36 St. Marks Rd. Henley-on-Thames Oxfordshire RG9 1LW Tel: +44 1491 411 859 Fax: +44 1491 572 305	Clinical monitoring and local project management support in Europe

CRO	Obligations Transferred
Fisher Scientific International, Inc. North America: Fisher Clinical Services Inc. 7554 Schantz Road; Allentown, PA 18106 Telephone: (610) 391-0800; Telefax: (610) 391-0801 Switzerland: Fisher Clinical Services AG Steinbuehlweg 69 CH-4123 Allschwil Switzerland Tel: +41 (0)61 485 2300; Telefax: +41 (0)61 485 2301	Central randomization
Exel U.K Business Office Ocean House The Ring Bracknell Berkshire RG12 1AN United Kingdom Drug Storage Location: Exel -Clinical Trials Logitics Cherwell 1 Middleton Close Banbury Oxon OX16 4RS. United Kingdom Contact Tel: +44 1295 228800/ +44 1295 228815	Study drug management and distribution in Europe and Australia

EXHIBIT L

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69,198

Skye Pharma Inc.
10450 Science Center Drive
San Diego, CA 92121

Attention: Schooley Gordon L., PhD
Senior Vice President

Dear Dr. Schooley:

Reference is made to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SKY0402.

Reference is also made to your January 6, 2005, request that this IND be placed on inactive status.

This IND is now considered to be on inactive status. Clinical studies may not be legally conducted under this IND.

Any request to initiate clinical studies under this IND must respond to the following issues.

1. Adequately designed non-clinical trials to support the proposed human clinical use according to the ICH-M3 *Guidance for Industry: Non-clinical studies for the conduct of human clinical trials for pharmaceuticals* are required. The non-clinical studies should utilize the same route of administration as the proposed human trials and should provide appropriate multiples of exposure based, preferably, on plasma concentrations. In this light, non-clinical studies in two (2) species (one rodent, one non-rodent) of adequate duration to the proposed clinical trial and utilizing a similar route and site of administration are required (e.g., wound infiltration and peripheral nerve blockade). The study designs should include clinical pathology (hematology, clinical chemistry, urinalysis), toxicokinetics, organ weights, and a full histopathological tissue evaluation. Acute single dose non-clinical studies should be designed with an acute (e.g., 24-48 hours, etc.) and 14-day observation and terminal euthanasia periods. Further, to support the different routes of anesthetic blockade it is prudent to conduct the non-clinical studies where the potential local toxicity is examined at the site of a nerve plexus rather than a single large diameter nerve.

2. Submit the final report for the 28-day repeat-dose toxicity study in the dog using the SKY-402 placebo study with the novel excipient dierucosylphosphatidyl-choline (DEPC). The study is required so that a complete toxicity evaluation of DEPC) can be assessed.

97732

3. If, in clinical studies, the drug is to come into contact with foreign items critical to the safety of the subject or outcome of the surgical procedure, the potential for reactivity of the drug with the material used in the foreign items should be determined. In the case of the hernia repair study, potential effects of the drug on the mesh used for stabilization or reinforcement of the repair should be examined.

4. In your proposed protocols, the nerve blocks with SKY0402 will be performed AFTER the patient has been anesthetized with general anesthesia. The consent form provided in the IND submission implies that this is the norm and makes no mention of performing the procedures (hernia repair or bunionectomy) under epidural, spinal or field block with local anesthesia. This would obviate the need for general anesthesia, but preclude participation in the study. You must either a.) stipulate that the need for general anesthesia is one of the inclusion criteria or b.) modify the informed consent form to reflect the other anesthetic options available to the patient.

In addition, we have the following comments and requests for additional information.

1. In the single-dose subcutaneous toxicity study of SKY0402 in rats (Inveresk Study 20995) a reduction in spleen weights was observed in both bupivacaine solutions. If nonclinical toxicology studies conducted in support of clinical protocols replicate this finding or demonstrate other indications of potential immune system effects further investigation of this phenomenon will be necessary during the course of drug development.

2. The drug product stability studies should include inverted vials and should begin prior to initiating the Phase 3 studies.

3. The temperature cycling conditions, to simulate use of the drug product, should be included in the stability studies.

4. In case the behavior of this product is similar to your DepoDur product (morphine sulfate extended-release liposome injection), we advise you to monitor free acids from the phospholipids (erucic, palmitic) in the drug product.

Clinical investigations under this IND may only be initiated (1) 30 days after FDA receives your request to initiate clinical studies, unless we notify you that the investigations described in your request are subject to a clinical hold, or (2) on earlier notification by us that the clinical investigations described in the request may begin.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
1/18/05 01:54:39 PM

EXHIBIT M

SkyePharma

March 7, 2006

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care and
Addictive Drug Products (HFD-170)
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

Attention: **Central Document Room**

Subject: **IND 69,198 (inactive); Serial #0010**
SKY0402 (bupivacaine extended-release liposome injection)
Other Names: sustained-release encapsulated bupivacaine; DepoBupivacaine

Request for Reactivation of IND 69,198

Dear Dr. Rappaport:

SkyePharma Inc. is hereby submitting information in support of our request to reactivate IND 69,198 for the purpose of initiating our Phase 3 program for SKY0402 (bupivacaine extended-release liposome injection). The overall goal of this program is to establish the safety and efficacy of a single dose of SKY0402 for prolonged post-operative analgesia following wound infiltration, peripheral nerve block, or epidural administration. The intra-articular route of administration is not part of the current clinical program, but may be considered for future clinical development. Reference is made to the initial IND (Serial #000; dated December 9, 2004) received by the Agency December 10, 2004 and the January 18, 2005 letter that inactivated IND 69,198.

As also noted at our meeting with the Division on January 11, 2006, SkyePharma plans to initiate a Phase 3 clinical development program with SKY0402. The following clinical studies were recently conducted in Europe and Australia:

> Protocol SKY0402-C-201: A Phase 2, Multicenter, Randomized, Double-Blind, Dose-Escalating/De-Escalating Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of a Single Dose of Sustained-Release Encapsulated Bupivacaine (SKY0402) in the Management of Post-Operative Pain in Subjects Undergoing Inguinal Hernia Repair

Protocol SKY0402-C-203: A Phase 2, Multicenter, Randomized, Double-Blind, Dose-Escalating/De-Escalating Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Sustained-Release Encapsulated Bupivacaine (SKY0402) Administered as a Nerve Block in the Management of Post-Operative Pain in Subjects Undergoing Bunionectomy

Protocol SKY0402-C-103: A Phase 1, Randomized, Double-Blind, Dose-Finding Study to Evaluate the Safety, Pharmacodynamic, and Pharmacokinetic Profile of Sustained-Release Encapsulated Bupivacaine (SKY0402) Administered via a Single Epidural Injection to Healthy Volunteers

These studies have completed enrollment. Available preliminary data from these studies, which are provided within Section 2.7 of this submission, support the continued clinical development of SKY0402.

As noted above, the overall goal of this program is to establish the safety and efficacy of a single dose of SKY0402 for prolonged post-operative analgesia following wound infiltration, peripheral nerve block, or epidural administration. The current general investigational plan is outlined in Section 1.13.9 of this submission. Following completion of the Phase 3 program outlined in Section 1.13.9, our goal is to submit a 505(b)(2) application for this product.

This submission includes the following Phase 3 protocol:

SKY0402-C-304: A Phase 3 Study to Evaluate the Efficacy and Safety of a Single Administration of SKY0402 for the Management of Post-Operative Pain in Patients Undergoing Inguinal Hernia Repair

The other clinical protocols mentioned in the general investigational plan will be submitted as protocol amendments following reactivation of the IND.

SkyePharma has also completed several nonclinical studies that were the subject of discussions and correspondence with the Division in the first half of 2005. Reference is made to the Agency's January 18, 2005 letter that inactivated IND 69,198, a March 30, 2005 teleconference to discuss additional nonclinical studies necessary to support the continued clinical development of SKY0402, SkyePharma's follow-up submission dated May 9, 2005 and Agency correspondence dated May 24, 2005 that concurred with our nonclinical study plans. The results of the entire nonclinical program are summarized in Section 2.6 of this submission; final and draft audited study reports are included in Module 4.

Each of the points raised in the Agency's letter of January 18, 2005, including nonclinical, clinical, and chemistry, manufacturing and controls topics, are provided below (in italics) followed by our responses:

1. *Adequately designed nonclinical trials to support the proposed human clinical use according to the ICH-M3 Guidance for Industry: Non-clinical studies for the conduct of human clinical trials for pharmaceuticals are required. The nonclinical studies should utilize the same route of administration as the proposed human trials and should provide appropriate multiples of exposure based, preferably, on plasma concentrations. In this light, non-clinical studies in two (2) species (one rodent, one non-rodent) of adequate duration to the proposed clinical trial and utilizing a similar route and site of administration are required (e.g., wound infiltration and peripheral nerve blockade). The study designs should include clinical pathology (hematology, clinical chemistry, urinalysis), toxicokinetics, organ weights, and a full histopathological tissue evaluation. Acute single dose non-clinical studies should be designed with an acute (e.g., 24-48 hours, etc.) and 14-day observation and terminal euthanasia periods. Further to support the different routes of anesthetic blockade it is prudent to conduct the non-clinical studies where the potential local toxicity is examined at the site of a nerve plexus rather than a single large diameter nerve.*

   SkyePharma has completed toxicology studies (listed below) in support of each route of administration proposed for clinical study. (Note that studies of the intra-articular route are also listed below and results are included within this submission. Even though intra-articular clinical studies are not part of the current clinical program, they may be considered for future clinical development.) The comprehensive study designs incorporate all of the Agency recommendations for studies of this nature. Summary results of each of these studies are included in Section 2.6.6.2.1. Draft audited study reports are included in Module 4.

   - Acute subcutaneous (surgical wound) and perineural toxicity studies of SKY0402 in rabbits (GLP; MPI Study 947-030) and dogs (GLP; MPI Study 947-029).
   - Acute epidural and intrathecal toxicity study of SKY0402 in dogs (GLP; MPI Study 947-020) and an acute epidural toxicity study of SKY0402 in rats (GLP; MPI Study 947-031).
   - Acute intra-articular toxicity study of SKY0402 in rabbits (GLP; MPI Study 947-035) and dogs (GLP; MPI Study 947-034).

   In addition, SkyePharma is developing protocols for the 1-month repeat-dose toxicity studies required for each route in support of the NDA. These protocols will be submitted for Agency review and comment.

2. *Submit the final report for the 28-day repeat-dose toxicity study in the dog using the SKY0402 placebo with the novel excipient dierucoylphosphatidylcholine (DEPC). This study is required so that a complete toxicity evaluation of DEPC can be assessed.*

   The results of the 28-day repeat-dose toxicity study of SKY0402 placebo in the dog are summarized in Section 2.6.6.3.3 of this submission; an audited draft study report

is included in Module 4, Section 4.2.3.2.2. The final report will be submitted within 120 days of initiation of the clinical studies and will include a summary of differences between the audited draft and final versions.

3. *If, in clinical studies, the drug is to come into contact with foreign items critical to the safety of the subject or outcome of the surgical procedure, the potential for reactivity of the drug with the material used in the foreign items should be determined. In the case of the hernia repair study, potential effects of the drug on the mesh used for stabilization or reinforcement of the repair should be examined.*

   A study of the compatibility of SKY0402 with the surgical meshes used in hernia repair has revealed no incompatibilities. Rectangular sheets of polypropylene mesh (Prolite, Atrium) and ePTFE mesh (Dulex, Bard) were treated with SKY0402 (15 mg/mL) or normal saline for 96 hours at 37°C. Mechanical properties of polypropylene and ePTFE meshes, as measured by suture retention strength and ball burst force, did not change after exposure to SKY0402 for 96 hours at 37°C. Similarly, measured SKY0402 product attributes (free bupivacaine, % PPV, pH, particle size and in vitro release) were not different compared to the control sample. Please refer to Section 2.3.P.2.6 for additional results of this study.

   Additionally, the interaction of SKY0402 and a surgical mesh that would typically be used in herniorraphy was evaluated as part of toxicology studies in the rabbit (MPI Study 947-030) and the dog (MPI Study 947-030). In these toxicology studies, hernia was surgically induced, then repaired, including use of a polypropylene surgical mesh. There were no adverse effects on wound healing. When SKY0402 was compared against bupivacaine HCl solution, there was no macroscopic nor histological evidence for any increase in local reactions or general exacerbations of bupivacaine toxicity. Additional discussion of these results is provided in Section 2.6.6.2.1 and in the draft audited study reports (Module 4).

4. *In your proposed protocols, the nerve blocks with SKY0402 will be performed AFTER the patient has been anesthetized with general anesthesia. The consent form provided in the IND submission implies that this is the norm and makes no mention of performing the procedures (hernia repair or bunionectomy) under epidural, spinal or field block with local anesthesia. This would obviate the need for general anesthesia but preclude participation in the study. You must either (a) stipulate that the need for general anesthesia is one of the inclusion criteria or (b) modify the informed consent form to reflect the other anesthetic options available to the patient.*

   Please refer to Protocol SKY0402-C-304 (Module 5, Section 5.3.5.1.1), Section 4.1 Inclusion Criteria, which specifies the following: "2. Scheduled to undergo unilateral, open-technique, tension-free, inguinal hernia repair under general or spinal anesthesia."

5. *In the single-dose subcutaneous toxicity study of SKY0402 in rats (Inveresk Study 20995) a reduction in spleen weights was observed in both bupivacaine solutions. If nonclinical toxicology studies conducted in support of clinical protocols replicate this finding or demonstrate other indications of potential immune system effects further investigation of this phenomenon will be necessary during the course of drug development.*

   SkyePharma believes that the apparent reduction in spleen weights observed in rats (Inveresk Study 20995) may be an experimental artifact due to age-related differences in body weight and small group size that make the interpretation of these data difficult.

   On a weight-adjusted basis, the reduction in spleen weight from control values was no longer apparent (i.e., when normalization was performed to account for age-related difference in spleen weight in relation to body size).

   There were no clinical pathology findings in this study (Inveresk Study 20995) that could be attributed to SKY0402. In addition, no effects on spleen weights could be identified following a 28-day repeat dosing schedule with SKY0402 placebo in rats (CRL Study LAB0001).

   SkyePharma is monitoring all nonclinical studies for effects on spleen weights or other indications of potential immune system effects. To date, no such effects have been observed.

6. *The drug product stability studies should include inverted vials and should begin prior to initiating the Phase 3 studies.*

   Stability data are being generated for lots 05-2502 (manufactured May 6, 2005) and 05-2503 (manufactured May 12, 2005) that are stored in both the inverted and upright positions. Stability data on these and other lots are provided in Section 2.3.P.8.3 of this submission.

   In addition, in the stability protocol for SKY0402 registration lots, vials in at least one lot will be stored in both inverted and upright positions (see Section 2.3.P.8.1.2 and Table 2.3.P.8.1-2).

7. *The temperature cycling conditions, to simulate use of the drug product, should be included in the stability studies.*

   Temperature cycling studies, including additional freeze-thaw studies at various temperatures and above-freezing cycling (e.g., 5°C/30°C), will be carried out on at least one lot.

8. *In case the behavior of this product is similar to your DepoDur product (morphine sulfate extended-release liposome injection), we advise you to monitor free acids from the phospholipids (erucic, palmitic) in the drug product.*

   Free fatty acids will be monitored during NDA-enabling stability studies.

Format/Organization of the Submission

This IND is provided in CTD format using the draft Table of Contents, "Comprehensive Table of Contents Heading and Hierarchy," provided by the Division on November 5, 2004. In some circumstances, information previously included in serial #000 is provided again for ease of review. Notations are made within the submission where this information is an exact duplication of information from the original submission.

All of the CMC information for SKY0402 is provided in Module 2, Section 2.3, Quality Overall Summary, therefore Module 3 has been omitted.

Audited draft toxicology reports are included in this submission. Final reports for all of these studies will be submitted within 120 days of the initiation of the clinical study and will include a detailed list of any changes that were made between the audited draft report and the final report.

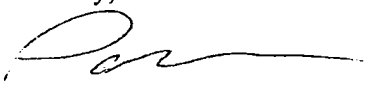
Reports of clinical studies SKY0402-C-103, SKY0402-C-201, and SKY0402-C-203 will be submitted to IND 69,198 as soon as they are available.

A comprehensive Table of Contents is provided in Section 1.2.2.

An original and two copies of this submission are being sent to the Central Document Room (Ammendale Rd., Beltsville, MD); two desk copies are also being sent to the attention of Kim Compton at your Silver Spring offices.

If you need additional information or have any questions, please contact me by telephone at 858-625-2414 x 3215, or by e-mail at Paula_Adams@SkyePharma.com.

Sincerely,



Paula C. Adams, PhD
Director, Regulatory Affairs

Enclosures

From: "Compton, Kimberly" <kimberly.compton@fda.hhs.gov>
To: "Paula Adams" <Paula_Adams@skyepharma.com>
Date: 3/20/2006 8:16:25 AM
Subject: ack ltr

20 MarL06

"MMS <skyepharma.com>" made the following annotations.

This secure message was sent using an SPN

==========

Hi Paula,

Attached is our ack of your resubmission for I 69, 198.

Thanks,
Kim
<<i 69-198 RE ack ltr 3-17-06.pdf>>
Kimberly Compton
Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products (HFD-170)
301-796-1191

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69, 198

SkyePharma, Inc.
10450 Science Center Drive
San Diego, CA 92121

Attention: Paula C. Adams, Ph.D.
Director, Regulatory Affairs

Dear Dr. Adams:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SKY0402 (sustained-release encapsulated bupivacaine).

We also refer to your submission dated March 7, 2006, serial number 010, received March 8, 2006, requesting to reactivation of this IND, which was inactivated prior to completion of its initial 30-day safety review.

As provided by 21 CFR 312.45(d), studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before April 7, 2006, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

If you have any questions call me at (301) 796-1191.

Sincerely yours,

{See appended electronic signature page}

Kimberly Compton, R. Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kimberly Compton
3/17/2006 07:16:48 PM

EXHIBIT N

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69, 198

SkyePharma, Inc.
10450 Science Center Drive
San Diego, CA 92121

RECEIVED
NOV 17 2006

Attention: Paula C. Adams, Ph.D.
Director, Regulatory Affairs

Dear Dr. Adams:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SKY0402 (sustained-release encapsulated bupivacaine).

We also refer to your submission dated March 7, 2006, received March 8, 2006, notifying us of your intent to reactivate this IND.

We have completed our review of your submission and have concluded that the clinical investigation(s) described in the protocol may begin. This IND is now considered to be on active status.

In addition, we have the following requests and recommendations.

1. Revise the following sections of the Informed Consent document:

    a. Add "Expect to receive only local anesthetic, or local anesthetic with sedation, epidural anesthetic or anesthetic other than general anesthesia or spinal anesthesia for my inguinal hernia operation." to the section that reads "WHAT CONDITIONS WILL MAKE ME NOT ELIGIBLE TO TAKE PART IN THE STUDY."

    b. Replace the section that now reads "An anesthesiologist will administer either spinal or general anesthesia to you. You will be signing a separate consent form, which will explain this procedure." with, "In an earlier discussion with your anesthesiologist, you have decided to accept either a general or spinal anesthetic for surgery to repair an inguinal hernia."

2. Revise the inclusion criteria to allow patients ASA IV patients or provide justification why these patients should not be included.

3. Specify the oxycodone product to be used for relief of severe post-operative pain in the protocol. The protocol must stipulate that only approved products (listed in the Orange Book) are allowed or full CMC, nonclinical and clinical safety data will need to be provided.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information (21 CFR 312.32(c)(2)); (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information (21 CFR 312.32(c)(1)); and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 796-1191.

Sincerely yours,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
11/13/2006 09:07:52 PM

EXHIBIT O

PACIRA
pharmaceuticals

September 28, 2010

Bob A. Rappaport, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia and Analgesia Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: NDA 22-496
Sequence No. 0000
SKY0402 (bupivacaine extended-release liposome injection)
Submission of Original New Drug Application

Dear Dr. Rappaport:

In accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.50 and 314.54, Pacira Pharmaceuticals, Inc. (Pacira) hereby submits an original New Drug Application (NDA 22-496) for SKY0402 (bupivacaine extended-release liposome injection) to be marketed under the proposed proprietary name EXPAREL™.

SKY0402 is an extended-release liposome injection of bupivacaine, an amide-type local anesthetic/analgesic, to be indicated for single-dose local administration into the surgical wound to produce postsurgical analgesia. SKY0402 is administered as a single dose by local infiltration into the surgical wound prior to the end of the surgical procedure. We are applying for approval of this product in the following strengths:

- 150 mg/10 mL single use vial.
- 300 mg/20 mL single use vial.

SKY0402's active ingredient (bupivacaine) has been marketed in the US for over 30 years as Marcaine® (bupivacaine HCl injection) and is listed as the Reference Listed Drug (NDA 16-964). Where appropriate, references to Marcaine and published literature are made to support sections not covered by the SKY0402 development program. A certification that there are no unexpired patents covering the Reference Listed Drug is provided in Section 1.3.5.2.

SKY0402's inactive ingredients include compendial excipients, non-compendial excipients that are used in US FDA-approved products, and one novel lipid excipient, dierucoylphosphatidylcholine (DEPC). The studies performed to qualify this lipid are presented in this NDA.

Pacira Pharmaceuticals Inc. | 10450 Science Center Drive | San Diego, CA 92121 | Tel: 858.625.2424 | Fax: 858.625.2439 | www.pacira.com

Pacira has conducted 21 clinical studies and one observational follow-up study to investigate SKY0402. Across these studies, a total of 1307 human subjects received SKY0402 at doses ranging from 10 mg to 750 mg and by various routes; this includes 823 subjects via the proposed administration route, wound infiltration.

Request for Priority Review

Pacira respectfully requests priority review status for this NDA. We believe SKY0402 to be an important treatment option for the management of postsurgical pain and per FDA guidance, meets the criteria for priority review classification on the basis that SKY0402 may "eliminate or substantially reduce a treatment-limiting drug reaction."

SKY0402 may serve as an alternative to opioid class products and can potentially reduce the volume and consumption of opioids otherwise used following surgical procedures; thus, eliminating the potential for opioid misuse. The FDA has acknowledged at a recent Advisory Committee meeting that "The misuse and abuse of the long-acting and extended-release opioid drug products have resulted in widespread and serious public health crisis of addiction, overdose, and health." Further, literature has shown that pain is most intense during the first 72 hours post surgery; thus, SKY0402 may serve as a viable alternative to treat postsurgical pain at a time when pain is most intense. As a result, a shift from opioid class products to SKY0402 could eliminate a large volume of opioids from reaching the general public and may prevent the subsequent potential for misuse. Per the FDA, a large proportion of the prescription opioid analgesics that are misused and abused are reportedly obtained by friends and relatives from patients with prescriptions.

Our clinical data supports not only the efficacy and safety of SKY0402 in the proposed indication, but clearly demonstrates its ability to reduce opioid consumption postsurgically.

In particular, in the pivotal Phase 3 hemorrhoidectomy study, SKY0402-C-316, the following secondary endpoints related to pain control and opioid-sparing were met:

- A significantly greater percentage of subjects in the 300 mg SKY0402 group versus subjects in the placebo group were pain free at 24 hours after surgery (58.5% versus 44.1%; p=0.0448) and at some other time points postdose (see ISE Appendix 6.1.3, ISE Table 6.4).

- A significantly lower percentage of subjects in the 300 mg SKY0402 group versus subjects in the placebo group received postoperative opioid pain medication at 24 hours (63.8% versus 88.2%; p<0.0001) and 72 hours (72.3% versus 90.3%; p=0.0007) and at other time points postdose (see ISE Appendix 6.1.3, ISE Table 7.4).

- Significantly less opioid pain medication was consumed by subjects in the 300 mg SKY0402 group versus subjects in the placebo group at 24 hours (5.379 mg versus 12.876 mg; p<0.0001), at 72 hours (9.949 mg versus 18.184 mg; p=0.0006), and at some other time points postdose (see ISE Appendix 6.1.3, ISE Table 8.4).

- The median time from the end of surgery to first use of supplemental opioid pain medication for subjects in the 300 mg SKY0402 group was significantly longer than for subjects in the placebo group (14.33 hours versus 1.17 hours, respectively; p<0.0001). See ISE Appendix 6.1.3, ISE Table 9.4.

Similarly, in the pivotal Phase 3 bunionectomy study, SKY0402-C-317, the following secondary endpoints related to pain control and opioid-sparing were met:

- The percentage of subjects who were pain free (NRS=0 or 1) for 120 mg SKY0402 compared to placebo was statistically significant at 2 hours (68.0% versus 45.8%; p=0.0019), 4 hours (38.1% versus 14.6%; p=0.0002), 8 hours (13.4% versus 3.1%; p=0.0078), and 48 hours (35.1% versus 19.1%; p=0.0153), but not at 12, 36, or 60 hours following study drug administration. See ISE Appendix 6.1.3, ISE Table 6.1.

- A significantly lower percentage of subjects in the 120 mg SKY0402 group versus subjects in the placebo group received postoperative opioid pain medication at 24 hours (92.8% versus 99.0%; p=0.0404). The percentage of subjects who received opioid rescue pain medication with 120 mg SKY0402 compared to placebo was also statistically significant at 8, 12, 16, and 20 hours, but not at 36, 48, or 60 hours postdose. See ISE Appendix 6.1.3, ISE Table 7.1.

- Significantly less opioid pain medication was consumed by subjects in the 120 mg SKY0402 group versus subjects in the placebo group at 24 hours (3.756 mg versus 4.655 mg; p=0.0077). See ISE Appendix 6.1.3, ISE Table 8.1.

- The median time from the end of surgery to first use of Percocet® (or generic oxycodone with acetaminophen) for subjects in the 120 mg SKY0402 group was significantly longer than for subjects in the placebo group (7.15 hours versus 4.28 hours, respectively; p<0.0001). See ISE Appendix 6.1.3, ISE Table 9.1.

In summary, in the pivotal trials, patients exposed to SKY0402 were less likely to use opioids, used fewer opioids when they were needed, and started taking them later in their hospital course while still maintaining an advantage regarding effective pain control. These advantages demonstrated that SKY0402 has the potential to allow patients to be discharged from the hospital or ambulatory center with fewer or no oral opioids. Data from supportive studies forms a body of evidence that supports this as well. Based upon the evidence presented, Pacira believes SKY0402 may clearly eliminate or substantially reduce a public health issue from the misuse of opioid-based treatments and thus satisfies the criteria for Priority Review classification. While Pacira understands that we may not meet the FDA's criteria to make an opioid sparing claim on the package insert, we do believe the evidence we have generated to be sufficient to justify a priority review classification for this NDA.

Other Regulatory Information

- The proposed proprietary name EXPAREL was previously submitted for FDA review on November 20, 2008 (reference is made to IND 69-198, Serial Number 0068). The

FDA granted Pacira approval to use the proprietary name EXPAREL on May 20, 2009, but noted that the continued use of this name would be further evaluated by FDA during the NDA review process. Please note that Pacira wishes to continue use of this proprietary name, EXPAREL, throughout the NDA review, approval, and commercial launch process.

- A request for deferral of pediatric studies is included in Section 1.9.2 of this submission. Deferral of pediatric studies was discussed previously with the FDA at the pre-NDA meeting held on February 16, 2010. The FDA has acknowledged that studies in the pediatric population should not begin until a complete assessment of safety and efficacy has been made in the adult population (see official pre-NDA meeting minutes dated 22 March 2010). Additionally, we are requesting to waive pediatric studies in children less than 2 years old, and a rationale for such request is outlined in Section 1.9.1.
- As requested by the FDA to assist the clinical reviewer's and the Division of Scientific Investigation's selection of clinical sites for inspection, a tabular summary of study information for each phase 3 clinical site is located in Section 1.11.4.
- In accordance with section 735 (379g) and 736 (379h) of the Federal Food, Drug, and Cosmetic Act, the user fee for I.D. number PD3010743 has been paid (see Section 1.1.3).
- To assist the NDA reviewers with particular administrative aspects of this submission, a "Reviewer's Guide" describing the organization, content, and completeness of the information presented is provided in Section 1.2.

This NDA submission contains all sections as required by 21 CFR Part 314.50 and is being submitted in accordance with the electronic format of the M4 International Conference on Harmonisation (ICH) Common Technical Document (CTD). The eCTD has been generated by Octagon Research Solutions Inc., who has filed an acceptable eCTD pilot with the Center on June 2, 2004 (Pilot Number 900024).

The confidentiality of this submission, and all information contained herein, is claimed by Pacira Pharmaceuticals, Inc. under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of Pacira.

We are open to meeting with the reviewers at the Division office to guide and familiarize them with the application and to answer any questions regarding this submission.

I will serve as Pacira's point of contact for this submission. If you have any questions regarding this submission, please contact me by telephone at (858) 625-2414 ext. 3262, by fax at (858) 558-6617, or by email at dwaina@pacira.com.

Sincerely,

Dwain K. Allen

Dwain K. Allen
Director, Regulatory Affairs

Electronic Submission Specifications

This submission is compliant with FDA's Guideline for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).

All electronic files included in this submission are provided on a single DVD and the electronic submission is approximately 4.10 GB. All files were checked and verified to be free of viruses.

Anti-Virus Program	Symantec Anti-Virus Edition
Program Version	8.1.0.825
Scan Engine Version	4.2.0.7
Virus Definition Date	09/23/2010 rev. 3
Submission Size	Approx. 4.10 GB

The IT point of contact for this submission is:

Name	Dwain Allen
Phone Number	858-625-2414 ext. 3262
Email Address	dwaina@pacira.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022496

NDA ACKNOWLEDGMENT

Pacira Pharmaceuticals, Inc.
10450 Science Center Drive
San Diego, CA 92121

Attention: Dwain K. Allen
Director, Regulatory Affairs

Dear Mr. Allen:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: SKY0402 (bupivacaine extended-release liposome injection)

Date of Application: September 28, 2010

Date of Receipt: September 28, 2010

Our Reference Number: NDA 022496

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 27, 2010 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia and Analgesia Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

If you have any questions, call Tanya Clayton, Senior Regulatory Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Tanya Clayton
Senior Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TANYA D CLAYTON
10/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022496

REVIEW EXTENSION – MAJOR AMENDMENT

Pacira Pharmaceuticals, Inc.
10450 Science Center Dr.
San Diego, CA 92121

Attention: Dwain Allen
Director, Regulatory Affairs

Dear Mr. Allen:

Please refer to your New Drug Application (NDA) submitted and received September 28, 2010, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Exparel (bupivacaine extended-release liposome injection).

On May 25, 2011, we received your May 25, 2011, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 28, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 30, 2011.

If you have any questions, call Sharon Turner-Rinehardt, Senior Regulatory Health Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARA E STRADLEY
06/13/2011

EXHIBIT P

	To	S/N	Description	Date	Vol	PCDocs#
1.	FDA		Pre-IND Meeting Request	7/15/02	1	79887
2.	FDA		Fax: Pre-IND Meeting Request (correction to NDA # ref)	7/18/02	1	
3.	File		Telephone Contact Report: Pre-IND meeting with FDA	7/24/02	1	80045
4.	File		Telephone Contact Report: Pre-IND meeting with FDA	7/24/02	1	80046
5.	FDA		Pre-IND meeting request – Questions for FDA	7/31/02	1	80123
6.	File		Telephone Contact Report: Confirmation of pre-IND meeting and structure of pre-IND briefing document	8/12, 8/13, 8/14	1	80395
7.	SKYE		Letter from FDA: Pre-IND meeting set for 10/2/2002	8/14/02	1	80686
8.	File		Telephone Contact Report: Submission of Pre-IND meeting package	8/30/02	1	80807
9.	FDA		Pre-IND Meeting Information Package	8/30/02	1	80102
10.	File		Telephone Contact Report – Revised Pre-IND meeting package	9/17/02	1	81073
11.	FDA		Fax to FDA: Revisions to Pre-IND meeting pkg	9/18/02	1	81306
12.	FDA		Pre IND Meeting Information Package Revision (pdf 81177)	9/18/02	1	81069
13.	File		SkyePharma Draft Minutes of 10/2/02 pre-IND Meeting at FDA (pdf 83641)	10/2/02	1	83639
14.	FDA		Meeting Request (Type C with Pharm/Tox Reviewer)	10/29/02	1	81666
15.	File		Telephone Contact Report: pre-IND mtg minutes and 10/29/02 Meeting request	11/11/02	1	82079
16.	File		Telephone Contact Report: 10/29/02 meeting request	12/12/02	1	82651
17.	File		Telephone Contact Report: Draft minutes of 12/19/02 Non-Clinical Teleconference	12/19/02	1	82814
18.	File		Telephone Contact Report: Kim Compton guidance on additional scientific advice from the Division	2/2/04	1	91785
19.	FDA		Request for Type B (Pre-IND) Meeting	6/4/04	1	93779
20.	SKYE		Email/Kim Compton: 2nd pre-IND Meeting Request, FDA requests questions package for FDA response prior to setting meeting date	7/12/04	1	95123
21.	FDA		Email to Kim Compton: SkyePharma to discuss FDA proposal and respond back to FDA	7/12/04	1	95124
22.	SKYE		FDA assigned pre-IND #69,198 and denies request for pre-IND meeting.	7/12/04	1	96464
24.	SKYE		Between S. Jensen and K. Compton: Original IND submission	10/07/04	1	102558
25	File		T/Con K Compton: Request for guidance on the format of an IND in CTD format	10/28/04 -11/3/04	1	91785
26	SKYE		Email from K Compton: TOC for IND CTD format, plus mapping of 312 and 314 regs item-by-item	11/5/04	1	96467

To	S/N	Description	Date	Vol	PCDocs#
FDA	**000**	Initial IND Submission Modules 1-3 FDA Vols. 1-3 Skye Vol. 2 Module 4 FDA Vols. 3-4 Skye Vol. 3 Module 4 FDA Vols. 5-6 Skye Vol. 4 Modules 4 FDA Vols. 7-9 Skye Vol. 5 Module 5 FDA Vols. 10-12 Skye Vol. 6 Module 5 FDA Vol. 13-14 Skye Vol. 7	12/9/04	2-7	
SKYE		Letter from FDA Receipt of IND 12/10/04 and assigns IND 69,198	12/10/04	8	97109
FDA	**001**	New Investigational Sites Protocols SKY0402C201 and SKY0402C203	12/23/04	8	97156
SKYE		E-Mail: Memo of needed information, CMC information for initial IND review	12/29/04	8	98200
SKYE		E-mail: Memo – Request for information to review IND submission	12/30/04	8	113266
FDA	**002**	Information Amendment: CMC – response to memo dated 29 Dec 04	12/30/04	8	97228
FDA		Fax to K. Compton containing SN003 Information Amendment: Clinical	12/30/04	8	106936
FDA	**003**	Information Amendment: Clinical	12/30/04	8	97233
SKYE		Email from KCompton to PAdams re: memo dated 01/04/05 and request for T-con for 01/06/05	1/5/05	8	98144
FDA		Email: confirmation of receipt of second clinical memo from Gordon, confirm that t/con at 8am PST/11am EST is fine, dial in numbers provided by SkyePharma	1/5/05	8	98145
SKYE		Email: confirmation of the requested T/Con dial in information	1/5/05	8	98146
FDA		Email to KCompton with SN004 attached and notification that hard copy will follow	1/5/05	8	98153
FDA	**004**	Information Amendment: Clinical and Protocol Amendment: New Investigator	1/5/05	8	101394
FDA	**005**	Request to Inactivate IND 69,198	1/6/05	8	98213
FDA		Email: Inactivation letter attached. List of Skye tcon attendees to follow in another e-mail	1/6/05	8	98149
SKYE		Email: List of FDA attendees at teleconference to discuss inactivation of IND 69, 198	1/6/05	8	98147
FDA		Email: List of SkyePharma attends at 1/6/05 teleconference to discuss inactivation of IND 69,198	1/6/05	8	98148
SKYE		Letter from FDA Confirms inactivation of IND 69,168 and instructions to initiate clinical studies	1/18/05	8	97732
SKYE		Email-re inactivation of ind 69,198 with follow up letter to Paula	1/19/05	8	107058

To	S/N	Description	Date	Vol	PCDocs#
FDA		Email-re inactivation of ind 69,198 (recd by Kimberly Compton)	1/19/05	8	107057
FDA	**006**	Type C Meeting Request (wk of March 21, 2005)	3/1/05	8	101398
SKYE		TCR: Notification of availability for Type C Meeting Request – 3/30/05 at 9:30 PST and alt. date of 4/7/05 at 12 EST	3/9/05	8	106928
SKYE		E-mail between K. Compton and T. Heyward regarding receipt of dial-in information for 3/30 T-con	3/9/05	8	106927
SKYE		E-Mail between T. Heyward and K. Compton regarding FDA participants at Bupi teleconference on 03/30/05	3/23/05	8	99066
SKYE		E-Mail between T. Heyward and K. Compton regarding additional participant at 3/30 t-con, listener only.	3/24/05	8	106929
FDA		Email to K. Compton from T. Heyward regarding title of Supervisory Pharmcologist at 3/30/05 telecon to discuss development of Bupivacaine	4/7/05	8	103850
SKYE		Email to T. Heyward from K. Compton regarding response to request to confirm title of supervisory pharmacologist	4/7/05	8	103851
FDA	**007**	IND 69,198 (Serial # 007) Type C Meeting Request	5/9/05	8	100161
SKYE		TCR: Clarification of study report being submitted as part of request to reactivate the IND	5/24/05	8	100119
SKYE		Email from K. Compton: attached FDA Response to Type C Meeting Request (denied)	5/24/05	8	106976
SKYE		Letter from FDA: Response to Type C Meeting Request (denied)	6/3/05	8	100134
FDA		E-Mail: Planning for new submissions to IND, sent to Division Doc Rm or Central Doc Rm on Ammendale Rd.	10/11/05	8	106978
SKYE		E-Mail: Correct address to send submissions is Ammendale Rd.	10/11/05	8	106977
FDA	**008**	Type B Meeting Request: End of Phase 2 Meeting	10/12/05	8	103789
SKYE		E-mail: Proposed meeting date (EOP2 meeting)	11/4/05	8	107607
SKYE		E-mail: Proposed meeting date, follow-up	11/8/05	8	107608
FDA		E-mail: Proposed meeting date, yes we accept proposed date – 1/11/06 at 3pm	11/8/05	8	107612
SKYE		E-mail: EOP2 date confirmed, send 3 standard copies and an additional 20 desk copies no later than 12/12/05	11/8/05	8	107613
FDA		E-mail: Acknowledgment of e-mail sent on 11/8/05 that states what is needed and by when	11/8/05	8	107614
FDA		E-mail: Meeting packages in the mail and should arrive on Monday the 12th with standard copies going to Central Document Room and 20 desk copies going to your attention.	12/9/05	8	105551
FDA		E-mail: Thought they were on their way but there seems to be a problem with the zip code. Fed Ex tells us that it is invalid	12/9/05	8	105560

To	S/N	Description	Date	Vol	PCDocs#
FDA		E-mail: Got your VM in time to switch the general zip code to 20903. Desk copies should get to you by Monday	12/9/05	8	105559
SKYE		E-mail: Sorry there was confusion. Will look for them on Monday	12/9/05	8	105558
FDA	**009**	Type B Meeting: End of Phase 2 Briefing Package	12/9/05	9	105155
FDA		Email-request for attendees at January 11 mtg and specific location of meeting	12/27/05	9	105843
FDA		Email-slides attached for meeting tomorrow	1/10/06	9	107600
SKYE		TCR: KCompton called and spoke with DWeinberger to make sure that the responses were received that Kim sent to PAdams via e-mail.	1/10/06	9	105685
FDA		Email-confirmation of responses and questioning confirming building number	1/11/06	9	107599
SKYE		Letter from FDA containing the official minutes from the meeting held on January 11, 2006 to discuss reactivation of IND and proceed with Phase 3 studies	2/9/06	9	106874
SKYE		E-mail: Plan to reactivate IND to initiate clinical studies in the US, will 2 desk copies be sufficient	2/15/06	9	106875
SKYE		Email: between PAdams and KCompton about plans to submit a request to initiate clinical studies and asked how many desk copies should be sent – reply that 2 should be OK	2/16/06	9	106866
FDA	**0010**	Request for Reactivation of IND 69,198 (mirrors FDA submission) • Volume 10 = Module 1 • Volume 11 = Module 2 • Volume 12 – 36 = Module 4 • Volume 37 – 41 = Module 5	3/7/06	10 – 41	
SKYE		Email-acknowledgement of request to reactivate IND – day 30 = April 7, 2006	3/20/06	42	107486
FDA		Email: Paula thanks KCompton for the e-mail acknowledgement	3/20/06	42	107437
SKYE		Letter- acknowledgement of request to reactivate IND – day 30 = April 7, 2006	3/23/06	42	107487
FDA	**011**	Protocol Amendment: Change in Protocol (SKY0402-C-304)	5/4/06	42	109860
FDA	**012**	General Correspondence: Requested Corrections and Clarifications of Meeting Minutes	5/4/06	42	109858
FDA	**013**	Information Amendment: Pharmacology-Toxicology (final audited toxicology reports submitted to replace draft reports submitted in SN010)	7/13/06	43 – 54	
FDA	**014**	Type A Meeting Request and Briefing Package – to discuss proposed changes to the Phase 3 development program.	7/21/06	55	111497

To	S/N	Description	Date	Vol	PCDocs#
FDA		E-mail: Please confirm receipt of Serial No. 014 Type A Meeting Request	7/28/06	55	112264
FDA	**015**	Protocol Amendment: New Investigator (304 – Chelly, Hartrick, Riley, Viscusi)	8/2/06	55	111719
FDA		TCR: K. Compton left message saying that rather than granting a meeting the Agency would respond in writing.	8/3/06	55	111937
SKYE		E-mail: Request for questions in word so as not to have to rewrite them	8/4/06	55	112265
FDA		E-mail: Questions attached as a word document	8/4/06	55	112266
FDA		E-mail: Please confirm if questions were received and also when can we expect the Division to respond?	8/16/06	55	112267
FDA		TCR: request for date of Division's internal meeting to review questions in SN 014 and likely timeframe for receipt of Division's written response	8/25/06	55	112474
SKYE		Email: Letter from FDA attached that outlines the responses to questions posed in a meeting request package dated 7/21/2006.	9/27/06	55	112970
SKYE		Letter: Outline of responses to questions posed in July 21, 2006 Meeting Request	9/27/06	55	112968
FDA		Email: Copy of SN016 attached; General Correspondence: Request for Clarification to comments supplied in response to our 7/21/06 Meeting Request	10/06/06	55	113025
FDA	**016**	General Correspondence: Request for Clarification of Responses to Type A Meeting Request	10/06/06	55	113024
FDA		Email: Recheck e-mail address and trying to resend e-mail from last Friday (pc doc 113024). Please confirm receipt. (In response to voice mail left by Kim Compton FDA Regulatory Project Manager)	10/11/06	55	113180
FDA		Email: Attempt to send again; asking for clarification of 2 pts in your response letter of 9/27/06. Please confirm receipt.	10/13/06	55	113181
FDA		TCR: Request for further clarification of Agency responses to our Type A meeting request	10/13/06	55	113203
FDA	**017**	103, 201, 203 Final Clinical Study Reports	11/13/06	55-74	103604
SKYE		Letter: (received 11/17/06) Review of IND reactivation complete clinical investigation may begin as described. Recommendations and requests include changes to the ICF and revision to the inclusion criteria	11/13/06	75	113721
FDA		Email: Status of SN016	11/27/06	75	113898
FDA		Email: Status of SN016 #2	11/27/06	75	113899
FDA		TCR: Summary of phone contacts re: SN016 – submission of clarification of 2 points from the Agencies response to our Type A meeting request (SN014)	11/28/06	75	113900

To	S/N	Description	Date	Vol	PCDocs#
FDA	**018**	Information Amendment: CMC – raw material and batch data for lot #'s 06-2502 and 06-2503 – we intend to use these lots in the PIII clinical trials	12/07/06	75	114175
FDA		Emails: Further follow-up with Kim Compton regarding responses to SN016 – clarification of 2 points (pediatric study/ies and dosing)	12/08/06	75	114328
FDA	**019**	General Correspondence: Change in ownership of an application	3/28/07	75	116117
FDA	**020**	Protocol Amendment: New Protocol SKY0402-C-207: A Multicenter, Randomized, Double-Blind, Parallel-Group, Active-Control, Dose-Ranging Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Primary, Unilateral, Inguinal Hernia Repair	5/8/07	75	116778
FDA	**021**	Protocol Amendment: New Protocol SKY0402-C-208: A Multicenter, Randomized, Double-Blind, Parallel-Group, Active-Control, Dose-Ranging Study to Evaluate the Safety, Efficacy and Comparative Systemic Bioavailability of a Single Administration of SKY0402 via Local Infiltration for Prolonged Postoperative Analgesia in Subjects Undergoing Total Knee Arthroplasty	5/31/07	75	117027
FDA	**022**	IND Annual Report	6/4/07	75	117082
FDA	**023**	Proposed Pediatric Study Request	6/6/07	76	117156
FDA	**024**	Change of Company Name to Pacira Pharmaceuticals, Inc.	6/20/07	76	117402
FDA	**025**	Protocol Amendment – New Protocol SKY0402-C-209 A Multicenter, Randomized, Double-Blind, Parallel-Group, Active-Control, Dose-Ranging Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Hemorrhoidectomy	6/21/07	76	117759
FDA	**026**	Protocol Amendment – New Investigators for Protocol SKY0402-C-207	6/29/07	76	
FDA	**027**	Protocol Amendment – New Protocol SKY0402-C-106 A Randomized, Single-Blind, Crossover Study to Evaluate the Safety and Onset of Action of SKY0402 Following Subcutaneous Administration in Healthy Volunteers	6/29/07	76	117701
FDA	**028**	Protocol Amendment New Protocol and Pediatric Plan for Sky0402	6/29/07	76	117764
FDA	**029**	Protocol Amendment Change in protocol sky0402 C 207	07/11/07	77	118039
FDA	**030**	SN030 Protocol amendment change in protocol sky0402 C 209	07/13/07	77	118038
FDA	**031**	Protocol Amendment – New Investigators for Protocol SKY0402-C-207 and SKY0402-C-209	07/30/07	77	118404
FDA		Email New Regulatory Contact at Pacira	08/08/07	77	122129

To	S/N	Description	Date	Vol	PCDocs#
FDA	**032**	Initial IND Safety Report 2007CT000033	08/15/07	77	118892
FDA		Notice of FDA Action	08/15/07	77	122131
FDA		Email Request for Feedback on SKY-0402-C-106	08/16/07	77	122130
FDA	**033**	Protocol Amendment – New Investigators for Protocol SKY0402-C-207 and SKY0402-C-209	08/27/07	77	119079
FDA	**034**	SKY0402-C-207 Protocol Amendment 2	09/25/07	78	122132
FDA	**035**	Protocol Amendment – New Investigators for Protocol SKY0402-C-209	09/25/07	78	119538
	036				
FDA	**037**	Protocol Amendment – New Investigators for Protocol SKY0402-C-207 SKY0402-C-208, and SKY0402-C-209	10/29/07	78	120044
Pacira		FDA Comments on SKY0402-C-106	11/13/07	78	120632
FDA	**038**	Protocol Amendment – New Investigators for Protocol SKY0402-C-207 SKY0402-C-208, and SKY0402-C-209	11/28/07	78	120519
FDA	**039**	Protocol Amendment 2- SKY0402-C-208	12/07/07	78	120651
FDA	**040**	Fax 7-Day Safety Report	12/20/07	78	120864
Pacira		FDA Response to Pediatric Written Request	12/27/07	78	121099
FDA	**041**	Protocol Amendment – New Investigators for Protocol SKY0402-C-106 and SKY0402-C-209	12/27/07	78	120881
FDA	**042**	Protocol Amendment , New Protocol (108)	01/14/08	78	122136
FDA	**043**	080121 Adverse Event Initial Report	01/21/08	79	121195
FDA	**044**	CMC Information Amendment Expiration Date Extension	01/22/08	79	121218
FDA	**045**	CMC Information Amendment (NOF DEPC)	01/23/08	79	121264
FDA	**046**	080129 New Investigator SKY-0402-C-108	01/29/08	79	121372
FDA	**047**	Type C Meeting Request	01/31/08	79	121412
FDA	**048**	New Protocol SKY0402-C-210	02/04/08	79	121439
FDA	**049**	Adverse Event Follow-up Report - #1 - 2007CT0000408	02/08/08	79	121527
FDA	**050**	Adverse Event Initial Report – 2008CT000010	02/25/08	79	121756
FDA	**051**	0802-27 New Investigator SKY-0402-C-208	02/27/08	79	121794
FDA	**052**	Protocol Amendment-New Investigators SKY0402-C-210	03/28/08	80	122355
FDA	**053**	Protocol Amendment-New Investigators SKY0402-C-208/210	05/15/08	80	123226
FDA	**054**	IND Annual Report 2008	06/06/08	80	122556
FDA	**055**	Protocol Amendment-New Investigators SKY0402-C-210	07/01/08	80	123953
FDA	**56**	Protocol Amendment-Change in Protocol	07/10/08	80	124052
FDA	**57**	Protocol Amendment-New Protocol (SKY0402-C-311)	07/14/08	80	124072
FDA	**58**	Protocol Amendment-New Protocol SKY0402-C-312)	07/14/08	80	124073
FDA	**59**	New Investigators SKY-0402-C-311 and 312	07/30/08	80	124297
FDA	**60**	New Investigators SKY-0402-C-311 and 312	09/05/08	80	124802

To	S/N	Description	Date	Vol	PCDocs#
FDA	**61**	New Investigators SKY-402-C-311 and 312	10/01/08	81	125130
FDA	**62**	CMC Information Amendment (Cambrex)	10/03/08	81	125162
FDA	**63**	Protocol Amendment-New Protocol (SKY0402-C-109)	10/16/08	82	125481
FDA	**64**	Protocol Amendment-New Protocol (SKY0402-C-315)	10/16/08	82	125482
FDA	**65**	Protocol Amendment-New Protocol (SKY0402-C-110)	10/16/08	82	125483
FDA	**66**	New Investigators SKY-0402-C-311	11/13/08	82	125881
FDA	**67**	New Investigators SKY-0402-C-312	11/13/08	82	125882
FDA	**68**	Request for FDA Evaluation of New Name	11/20/08	82	126062
FDA	**69**	Protocol Amendment-New Protocol (SKY0402-C-211)	11/21/08	82	126063
FDA	**70**	Protocol Amendment, New Investigators,SKY-0402-C-211	01/06/09	82	126339
FDA	**71**	Protocol Amendment, New Investigators, Simple TKA 311	01/06/09	83	126340
FDA	**72**	Protocol Amendment, New Investigators, Simple Hem 312	01/06/09	83	126341
FDA	**73**	Protocol Amendment, New Investigators, Simple BA 315	01/06/09	83	126342
FDA	**74**	Protocol Amendment, New Investigators, SKY0402-C-109	01/06/09	83	126343
Pacira		Email Chain with FDA re: Pre-Assigned NDA Number (22-496)	01/07/09	83	126561
Pacira		Email Chain with FDA re ongoing studies	01/15/09	83	126562
Pacira		Email Chain with FDA re ongoing studies	01/15/09	83	126563
FDA		Email Chain with FDA re ongoing studies	01/19/09	83	126564
Pacira		Email Chain with FDA re ongoing studies	01/23/09	83	126565
FDA	**75**	Protocol Amendment, New Investigators, Simple BA 315	02/04/09	83	126674
FDA	**76**	Protocol Amendment, New Investigators, SKY-0402-C-110	02/04/09	83	126675
FDA	**77**	Protocol Amendment, SKY-0402-C-317, New Protocol	04/28/09	84	127245
FDA		Email to Kim Compton, re: Update to IND 69,198	04/24/09	84	127441
FDA	**78**	Protocol Amendment, SKY-0402-C-317, New investigators	05/07/09	84	127317
FDA		Email to Kim Compton, re: Follow-up Update to IND 69,198	05/13/09	84	127442
FDA	**79**	Protocol Amendment – New Protocol, SKY0402-C-316	06/02/09	84	127655
FDA	**80**	Annual Report 2009	06/08/09	84	127677
FDA	**81**	Protocol Amendment – New Protocol, SKY0402-C-110	06/11/09	84	127710
FDA	**82**	Protocol Amendment - New Investigator, SKY0402-C-316	06/22/09	85	127828
Pacira		Letter from FDA re: SKY0402-C-315	07/02/09	85	127873
FDA		Email to Kim Compton re: Comments to IND 69,198	07/22/09	85	128208
FDA	**83**	Revised Investigator's Brochure	08/07/09	85	128203
FDA	**84**	Protocol Amendment - New Investigators, SKY0402-C-316	08/11/09	85	128231
FDA	**85**	Response to FDA – RE: SKY-0402-C-315	08/12/09	85	128273
FDA	**86**	Type B Meeting Request (pre-NDA)	09/28/09	85	128674
FDA		Email Clinical Studies Status update	09/28/09	85	128680

To	S/N	Description	Date	Vol	PCDocs#
FDA	**87**	IND Adverse Event Follow-up Report 2007CT000033	10/27/09	85	128914
Pacira		FDA Letter, RFI re EXPAREL Clinical Program Email received 11/4/09, Letter received 11/24/09	11/3/09	85	128990
FDA	**88**	Briefing Book (pre-NDA) Meeting Date 16 Feb 2010	01/07/10	86	129351
FDA	**89**	Information Amendment - Clinical Study Reports	01/15/10	87	129379
FDA	**90**	Placebo Samples	02/01/10	87	129465
FDA		SN:0090 Rescinded (sent as desk copy)	02/01/10	87	129465
FDA	**90**	Protocol Amendment – New Protocol (318)	02/25/10	87	129647
FDA	**91**	IND Adverse Event Report Follow-up #2	03/04/10	87	129730
FDA	**92**	Information Amendment - Toxicology	03/05/10	87	129737
FDA	**93**	Protocol Amendment - New Investigators (318)	03/18/10	87	129863
FDA	**94**	Response to FDA Letter Dated 03 November 2009	03/19/10	87	129887
Pacira		Email – Minutes from K. Compton Comments form Statistician	03/17/10	87	130222
Pacira		Meeting Minutes – (Meeting 16 Feb 2010, pre-NDA)	03/22/10	87	130105
Pacira		Email – Minutes from K. Compton pre-NDA meeting	03/25/10	87	130104
Pacira		Email – Minutes from K. Compton pre-NDA meeting	04/02/10	87	130106
FDA	**95**	General Correspondence – Response to FDA email dated 3/17/2010	05/14/10	87	130228
FDA	**96**	2010 - IND Annual Report	06/07/10	87	130369
FDA	**97**	Information Amendment – Clinical Study Reports	11/02/10	88	131603
FDA		Email – follow up to SN 0097	11/05/10	88	TBA
Pacira		Email – FDA acknowledging receipt of SN 0097	11/08/10	88	TBA
FDA	**98**	IND Adverse Events	10/14/10	88	131880
FDA	**99**	2011 - IND Annual Report	06/06/11	88	TBA
FDA	**100**	Protocol Amendment – New Protocol (SKY0402-C-111)	07/28/11	88	TBA
Pacira		Email – Information request regarding protocol SKY0402-C-111	08/11/11		TBA
FDA	**101**	Protocol Amendment – New Protocol (open-col, 301)	08/25/11	88	TBA
FDA	**102**	Protocol Amendment – New Protocol (TAP, 701)	08/25/11	88	TBA
FDA		Email – Logistics regarding CMC update to IND file	09/07/11	88	TBA
FDA	**103**	Response to FDA IR dated 8/11/11	09/14/11	88	TBA
FDA	**104**	Protocol Amendment – New Protocol (lap-col, 601)	10/10/11	89	TBA
FDA	**105**	Protocol Amendment – New Protocol (lap-col, 605)	10/13/11	89	TBA
FDA	**106**	Protocol Amendment – New Protocol (open-col, 303)	10/13/11	89	TBA
FDA	**107**	Protocol Amendment – New Protocols (open-col, 302 and lap-col, 602)	10/19/11	89	TBA
FDA	**108**	Protocol Amendment – New Protocols (Ileostomy-reversal, 501)	11/02/11	89	TBA

To	S/N	Description	Date	Vol	PCDocs#
FDA	**109**	Information Amendment – CMC update to align with commercial process	12/09/11	89	TBA
FDA	**110**	Protocol Amendment – New Protocols (lap-col, 504 and lap-col, 606)	12/09/11	89	TBA

EXHIBIT Q

NDA 22-496
EXPAREL (bupivacaine extended-release liposome injection)

No.	Originator Org.	person	Format	Date	Topic	Description	resolution (if applicable)	Pcdoc No.	Status (open/closed)	NDA amendment planned? Yes / No (Seq.)
1	Pacira	n/a	eCTD	9/28/2010	admin	Initial NDA submission	n/a	NDA-reader	n/a	0000
2	FDA	n/a	letter	9/28/2010	admin	Stamped receipt of NDA	n/a	131226	n/a	n/a
3	FDA	SP	TCR	10/12/2010	regional	Division requested for contact info for API suppliers	Pacira provided requested information via email on 10/12/10	131227 131534	closed	(0001, 11/9/10)
4	FDA	SP	phone	10/18/2010	regional	Division request for contact info for API, BASF (France site)	Pacira provided requested information via email on 10/19/10	131535 131536	closed	(0001, 11/9/10)
5	FDA	Tanya	email	10/18/2010	admin	Tanya introduces herself as FDA PM for EXPAREL	n/a	131570	n/a	n/a
6	FDA	CRB	email/v-mail	10/21/2010	e-sub	FDA eSubs team was unable to access many of the eCTD files in NDA	Octagon Solutions delivered new eCTD to FDA eSub team on 10/22/10	131537 131538 131539	closed	No
7	FDA	Tanya	email	10/22/2010	pharm/tox	Division requested comprehensive list of all nonclinical studies and M4 literature	Pacira provided requested information via email on 10/25/10	131707 131709	closed	(0001, 11/9/10)
8	FDA	Tanya	email/letter	10/27/2010	admin	Tanya sends the FDA NDA acknowledgment letter as attachment	n/a	131708 131712	n/a	n/a
9	FDA	Tanya	email	11/1/2010	efficacy	Division requested SKY0402 lot numbers for all clinical and nonclinical studies.	Pacira provided requested information via email on 11/2/10	131713 131709	closed	(0001, 11/9/10)
10	FDA	Tanya	email	11/5/2010	regional	Division requested that we formally file our proprietary name review request to the NDA file.	Pacira provided requested info via Amend. on 11/12/10)	131710	closed	(0002, 11/12/10)
11	FDA	Tanya	email	11/15/2010	regional	Division seeks clarification re: Financial Disclosure Info for all clinical investigators.	Pacira provided requested info via Amend.	131711	closed	(0003, 11/18/10)

No.	Originator Org.	Originator person	Format	Date	Topic	Description	resolution (if applicable)	Pcdoc No.	Status (open/closed)	NDA amendment planned? Yes / No (Seq.)
12	FDA	Virgilio	phone	11/16/2010	quality	Division requested nitrogen lot info (LN & release data) for nitrogen used to manf. EXPAREL batches used for clinical/stability.	Pacira provided requested info via fax to field officer (Virgilio Pacio)	131750 131722 131752	closed	fax, 11/17/10
13	FDA	Tanya	email	11/17/2010	quality	Division requested particulate matter, endotoxin, sterility testing for commercial lots and side-by-side comparison of equipment differences of 25L, 45L, and commecial scale	Pacira provided info via email on 11/21/10 and will f/u with amendment (0004).	131721 131751	closed	(0004, 11/24/10)
14	FDA	Tanya	email	11/22/2010	regional	Division requested clarification re: financial disclosure info for clinical investigators	Pacira responded via email on 11/22/10 and clarified that the financial certification is a "blanket certification" and covers all studies and investigators.	131770 131781	closed	No
15	FDA	Tanya	email	11/22/2010	quality	Division in response to Pacira's 11/21 email is requesting a t-con to discuss microbiology info.	T-con held 11/23 (9:00AM PST). Please see meeting minutes for details.	TCR in draft	closed	No
16	FDA	Tanya	email	12/7/2010	regional	Division requested official Patent cert. Form 3542a and "highlights" section of draft labeling text (PI).	Form 3342a submitted via Amendment. Pacira to clarified that "highlights" already part of original application via separate email (on 12/8)	in draft	closed	Yes (0005, 12/9/10)
17	FDA	Tanya	email	12/10/2010	regional	Division followed-up with request for "highlights" section for PI; requested two-column format per guidance.	Pacira follows-up with status and timing of 2-column format on 12/17/10. Octagon to prepare MS word and SPL in 2-column format.	131902 131924	closed	Yes (0006, 12/22/10)

No.	Originator Org.	person	Format	Date	Topic	Description	resolution (if applicable)	Pcdoc No.	Status (open/closed)	NDA amendment planned? Yes / No (Seq.)
	FDA	Tanya	letter	12/10/2010	admin	Tanya sends the official Filing letter via email, which requested the following information:	Pacira follows-up with email on 12/13/10 to confirm that these can be answered and submitted individually.	131899 131925	n/a	
18						IR # 1: Percent free bupivacaine specification	See amendment		closed	Yes (0008, 2/1/2011)
19						IR # 2: Nonclinical bridge to RLD	See amendment		closed	Yes Seq-0010
20						IR # 3: Process validation data for commercial scale	See amendment (**Media runs excluded from initial AVP - seq-0018**)		closed	Yes (0018, 4/18/2011) (0023, 5/25/2011 - media runs)
21						IR # 4: Drug Master Files	See amendment		closed	Yes (0008, 2/1/2011)
22						IR # 5: Bupivacaine free base equivalent	See amendment		closed	Yes (0008, 2/1/2011)
23						IR # 6: Level of metal content in drug product	See amendment		closed	Yes (0010, 2/9/2011)
24						IR # 7: Leachable levels in NDA batches	See amendment		closed	Yes (0014, 3/17/2011)
25						IR # 8: Clean air/Nitrogen	See amendment		closed	Yes (0008, 2/1/2011)
26						IR # 9: Vial rejection	See amendment		closed	Yes (0008, 2/1/2011)
27						IR # 10: Freeze thaw validation data	See amendment		closed	Yes (0008, 2/1/2011)
28						IR # 11: In vitro release specifications	See amendment		closed	Yes (0012, 2/24/11)

No.	Originator Org.	Originator person	Format	Date	Topic	Description	resolution (if applicable)	Pcdoc No.	Status (open/closed)	NDA amendment planned? Yes / No (Seq.)
29						IR # 12: In vitro release profile comparisons	See amendment		closed	Yes (0008, 2/1/2011)
30	FDA	John Lee	phone	12/15/2010	regional	John called Pacira to requests clinical site info for phase 3 clinical studies (similar to DSI requests made during pre-NDA meeting)	Pacira verbally directed John to where he could find the requested information within the current eCTD backbone.	131891	closed	No
31	FDA	John Lee	email	12/22/2010	regional	John emailed to ask for help with finding the "subject data listing for concomitant medications" in Study SKY0402-C-316.	Pacira responded via email on 12/23/10. John Lee acknowledged receipt via email on 12/23/10 and was satisfied with our response.	131948 132026	closed	No
32	FDA	Tanya Clayton	email	1/4/2011	efficacy	Division is requesting additional information regarding the QT studies (105/107).	Pacira acknowledges recepit on 1/7; response pending.	132027	closed	Yes (0009, 2/4/11)
33	FDA	Percilla Johnson	email	1/12/2011	regional	Division informed Pacira on which clinical sites have been selected for GCP inspection.	Pacira acknowleged receipt on 1/17/11; Pacira has confirmed availability of each site, travel arrangements are pending.	132135 132137 132138 132139 132140	closed	No
34	FDA	Swati Padwardhan	email	1/14/2011	quality	CM&C Reviewer provides feedback regarding the in vitro dissolution methods and acceptance criteria.	Pacira acknowledged recepit on 1/14; response pending.	132136 132573	closed	Yes (0012, 2/24/11)
35	FDA	Sharon Turner-Rinehardt	email	1/20/2011	quality	Division sends IR regarding n-butylbromide acceptance limits set for API supplier Cambrex.	Pacira acknowledged recepit on 1/20; response to IR pending.	132171 132172	closed	Yes (0016, 3/7/11)

No.	Originator Org.	Originator person	Format	Date	Topic	Description	resolution (if applicable)	Pcdoc No.	Status (open/closed)	NDA amendment planned? Yes / No (Seq.)
36	FDA	Sharon Turner-Rinehardt	email	1/20/2011	regional	Division sends IR seeking clarification on location of 317 dataset containing the raw pain intensity score for each patient.	Pacira acknowledged receipt on 1/20; Pacira follows-up with location via email to PM on 1/25/11.	132172	closed	No (addressed via email)
37	FDA	Carol Holquist / DMEPA	letter	2/16/2011	regional	Division of Medication Error Prevention and Analysis sends letter preliminarily approving treadename, EXPAREL	none	132420	closed	No
38	FDA	Sharon Turner-Rinehardt	email	2/17/2011	regional	Sharon sends requests regarding formatting changes to the draft labeling text to be consistent with PLR.	Pacira acknowledges email on 2/18 and provides revised labeling text. Sharon f/u 2/18 to say formatting is still not per PLR. Pacira provides 2nd revision 2/22, which Sharon latter confirmed it complies.	132422	closed	Yes (0013, 3/2/11)
39	FDA	Sharon Turner-Rinehardt	email	3/1/2011	efficacy	Sharon sends requests regarding ecg-waveforms submitted to the warehouse.	Pacira sends response via email on 3/2/11.	132574 132575	closed	No
40	FDA	Swati Padwardhan	email	3/10/2011	quality	Swati sends email to notify Pacira that DMF holders rec'd FDA IRs.	Pacira acknowledges receipt on 3/16 and states intention to f/u with each DMF holder.	132644 132645 133298	n/a	No
41	FDA	Sharon Turner-Rinehardt	email	3/25/2011	efficacy	Sharon sends IR regarding several topics including: blinding procedures; sample of DP; CRFs for Pts of interest; CNS/CV AE listing.	Pacira acknowledges email on 3/29 and asks for clarification on timing of IR. Sharon responds later that day 3/29.	133285	closed	Yes (0015, 4/5/11) (0017, 4/14/11 - f/u missing CRF)

No.	Originator Org.	person	Format	Date	Topic	Description	resolution (if applicable)	Pcdoc No.	Status (open/closed)	NDA amendment planned? Yes / No (Seq.)
42	FDA	Sharon Turner-Rinehardt	email	4/8/2011	quality	Sharon sends email to request T-con with Pacira re: PAI on 4/11/11	Pacira acknowledges and agress to tele-con. T-con occurred 4/11/11.	133296	closed	No
43	FDA	All	TCR	4/11/2011	quality	Tele-con regarding PAI readiness and timing.	PAI schedule for early June, FDA welcomes submitting AVP excluding media runs but prefers complete package. FDA also states they are unable to inspect Japanese DEPC suppliers, and as a result, they've asked us to remove from NDA - Pacira intends to respond and counter DEPC supplier concerns.	133288	closed	Yes (0020, 5/5/11)
44	FDA	Sharon Turner-Rinehardt	email	4/21/2011	quality	Sharon sends IR requesting validation report for the SIP package		133297	closed	Yes (0019, 4/27/11)
45	FDA	Sharon Turner-Rinehardt	email	5/6/2011	quality	Sharon sends IR, requesting an executed batch record for a commerical batch.	Pacira replies 5/9 to inform FDA that batch record will be sent via email and followed up with formal amendment. Record sent via email on 5/10 and receipt rec'd confirmation from Sharon on 5/11.	133290 133293	closed	Yes (0021, 5/13/11)
46	FA	Swati Padwardhan	email	5/9/2011	quality	Swati sends email to notify Pacira that DMF holders rec'd FDA IRs. (see also email from swati on 3/10/11)		133291	n/a	No

No.	Originator Org.	Originator person	Format	Date	Topic	Description	resolution (if applicable)	Pcdoc No.	Status (open/closed)	NDA amendment planned? Yes / No (Seq.)
47	FDA	Swati Padward han	email	5/9/2011	quality	Swati asks for clarification with regards to DEPC DPPG and Trioctanoin release testing procedures.	A copy of the amendment was sent to Swati via email on 5/20/11.	133292	closed	Yes (0022, 5/20/11)
48	FDA	Swati Padward han	email	5/17/2011	quality	Swati emails to f/u with seq-0021 and to request data on 2,6 dimethylaniline (DMA) levels.	Pacira acknowledges receipt on 5/17 and request brief t-con with CMC reviewer. Swati responds on 5/17; acceptance of t-con up to CMC reviewer.	133294 133295	closed	Yes (0024, 6/14/11)
49	FDA	Swati Padward han	email	6/2/2011	quality	Swati emails to clarify number of vials used for release testing	Pacira responds via email on 6/2 and Swati acknowledges receipt on 6/3.	133741 133742	closed	No (addressed via email)
50	FDA	Prasad Peri	letter	6/3/2011	quality	Dr. Peri sends letter ID'ing 5 separate lrs all having to do with biopharm and in-vitro release.	Pacira acknowledges receipt and request clarification on 6/6; FDA responds 6/7. On 6/8 FDA requests tcon for 6/9. Tcon occurs 6/9; Pacira f/u on 6/10.	133743 133744 133745 133746	closed	Yes (0031, 7/27/11)
51	FDA	Swati Padward han	email	6/15/2011	quality	Swati requests clarification on in vitro sampling and requests USAN for bupivacaine.	Pacira responds on 6/15 addressing the sampling query, but requests clarification on the USAN query. FDA f/u on 6/20.	133749 133750 133751	closed	Yes (0030, 7/26/11) (0037, 9/13/11)
52	FDA	Swati Padward han	email	6/21/2011	quality	Swati requests clarification on butyl bromide testing for DS supplier, BASF.	Pacira sends NDA amendment.	133752	closed	Yes (0028, 7/22/11)

No.	Originator Org.	person	Format	Date	Topic	Description	resolution (if applicable)	Pcdoc No.	Status (open/closed)	NDA amendment planned? Yes / No (Seq.)
53	FDA	Sharon Turner-Rinehardt	email	6/23/2011	quality	Sharon send requests asking for media fill protocol(s) used to simulate the commercial aseptic manuf. (including pooling)	Pacira responds via email on 6/27 and sends follow-up Amend (seq 0025) on 7/1.	133753 133754	closed	Yes (0025, 7/1/11)
54	FDA	Swati Padwardhan	email	8/9/2011	quality	FDA requests clarification re: discrepancies between the values for the in vitro release assay.	Pacira responds via email on 8/12 date.	TBA	closed	No (addressed via email)
55	FDA	Sara Stradley	letter	8/9/2011	labeling	FDA's DMEPA sends DR letter (with list of deficiencies) closing out their review of the vial and carton labels.	Pacira sends NDA amendment.	TBA	closed	Yes (0035, 8/31/11 - 9/6/11)
56	FDA	Swati Padwardhan	letter	8/18/2011	quality	FDA CMC review team sends DR letter (with list of deficiencies) closing out their review.	Pacira requests t-con to clarify certain items listed (on 8/19). T-con held 8/29.	TBA	closed	Yes (0033, 8/26/11) (0034, 9/2/11)
57	FDA	Swati Padwardhan	email	9/2/2011	quality	Swati sends email requesting to lower DMA specs to NMT 0.05% (LLOQ) and to provide stability info on clinical batches	Pacira acknowledges email 9/9.	TBA	closed	Yes (0036, 9/12/11)
58	FDA	Parinda Jani	letter	9/7/2011	admin	FDA sends letter to inform of ongoing investigation with Cetero and potential implications with open NDAs	Pacira will respond with formal letter stating that no business has ever been done with Cetero to support EXPAREL	TBA	closed	Yes (0040, 9/26/11)
59	FDA	Swati Padwardhan	phone	9/16/2011	quality	Swati calls to discuss issues with nitrogen testing vendor ECA	Pacira responds via email and phone on 9/16 and commits to remove ECA from NDA	TBA	closed	Yes (0038, 9/20/11)

No.	Originator Org.	Originator person	Format	Date	Topic	Description	resolution (if applicable)	Pcdoc No.	Status (open/closed)	NDA amendment planned? Yes / No (Seq.)
60	FDA	Sharon Turner-Rinehardt	email	9/20/2011	quality	Sharon informs Pacira that vol. 2 of seq 0019 was not rec'd by FDA esubs	Pacira responds same day with commitment to correct ASAP.	TBA	closed	Yes (0039, 9/23/11)
61	FDA	Sharon Turner-Rinehardt	email	9/21/2011	efficacy	Sharon sends IR regarding foreign data and 315 study termination	Pacira responds to IR via email same day	TBA	closed	No (addressed via email)
62	FDA	Swati Padwardhan	email	9/21/2011	quality	Swati sends IR regarding lipid stability	Pacira acknowledges receipt same day.	TBA	closed	Yes (0041, 9/26/11)
63	FDA	Sharon Turner-Rinehardt	email	9/23/2011	efficacy	Sharon sends IR requesting clarification on bioanalytical methods used to report PK values	Pacira sends NDA amendment.	TBA	closed	Yes (0042, 9/29/11)
64	FDA	Sharon Turner-Rinehardt	email	9/30/2011	regional	Sharon sends first round of FDA proposed PI changes	Pacira requests t-con on 10/6/11, which is denied same day. Pacira submits proposed changes to PI via email on 10/7/11 (draft 1).	TBA	closed	No (addressed via email)
65	FDA	Sharon Turner-Rinehardt	email	10/3/2011	regional	Sharon sends IR regarding proposed carton/vial edits and clarification on indicators	Pacira responds via email on 10/7/11.	TBA	closed	No (addressed via email)
66	FDA	Sharon Turner-Rinehardt	email	10/4/2011	regional	Sharon informs Pacira that the patent certification is incorrect	Pacira sends NDA amendment.	TBA	closed	Yes (0043, 10/17/11)
67	FDA	Sharon Turner-Rinehardt	email	10/13/2011	regional	Sharon informs Pacira that pediatric waiver for under declined, requests Pacira to submit revised proposal re: ped study timing including under two age group	Pacira sends NDA amendment.	TBA	closed	Yes (0044, 10/17/11)

No.	Originator Org.	person	Format	Date	Topic	Description	resolution (if applicable)	Pcdoc No.	Status (open/closed)	NDA amendment planned? Yes/ No (Seq.)
68	FDA	Sharon Turner-Rinehardt	email	10/13/2011	quality	Sharon sends IR regarding temparature indicator data	Pacira sends NDA amendment.	TBA	closed	Yes (0045, 10/24/11)
69	FDA	Sharon Turner-Rinehardt	email	10/13/2011	regional	Sharon sends coutesy update regarding label negotiations status	Pacira acknowledges receipt same day.	TBA	n/a	n/a
70	FDA	Sharon Turner-Rinehardt	email	10/18/2011	regional	Sharon sends 2nd round of FDA proposed PI changes	Pacira submits proposed changes to PI via email on 10/20/11 (draft 2).	TBA	closed	No (addressed via email)
71	FDA	Sharon Turner-Rinehardt	email	10/21/2011	regional	Sharon sends request for T-con to discuss PI on 10/24	Pacira sends email accepting t-con request. Pacira submits proposed changes to PI via email on 10/24/11 (draft 3).	TBA	closed	No (addressed via email)
72	FDA	Sharon Turner-Rinehardt	email	10/25/2011	regional	Sharon sends request for T-con to discuss PI futher on 10/25	Pacira sends email accepting t-con request. Pacira submits proposed changes to PI via email on 10/25/11 (draft 4).	TBA	closed	No (addressed via email)
73	FDA	Sharon Turner-Rinehardt	email	10/26/2011	regional	Sharon sends 3rd round of FDA proposed PI changes	Pacira submits proposed changes to PI via email on 10/26/11 (draft 5).	TBA	closed	No (addressed via email)
74	FDA	Sharon Turner-Rinehardt	email	10/27/2011	regional	Sharon sends 4th round of FDA proposed PI changes	Pacira submits proposed changes to PI via email on 10/27/11 (draft 6).	TBA	closed	No (addressed via email)
75	FDA	Sharon Turner-Rinehardt	email	10/27/2011	regional	Sharon sends request to edit vial label	Pacira accepts edits and submits final labeling on 10/28.	TBA	closed	No (addressed via email)

No.	Originator Org.	Originator person	Format	Date	Topic	Description	resolution (if applicable)	Pcdoc No.	Status (open/closed)	NDA amendment planned? Yes / No (Seq.)
76	FDA	Sharon Turner-Rinehardt	email	10/27/2011	regional	Sharon sends request to increase est name prominence	Pacira accepts edits and submits final labeling on 10/28.	TBA	closed	No (addressed via email)
77	FDA	Sharon Turner-Rinehardt	email	10/27/2011	regional	Sharon sends final pediatric postmarket requirement	Pacira accepts PMR on 10/27/11.	TBA	closed	No (addressed via email)
78	FDA	Sharon Turner-Rinehardt	letter	10/28/2011	regional	FDA sends official NDA approval letter	n/a	TBA	n/a	n/a
79	Pacira	RA	eCTD	11/11/2011	regional	Pacira sends final printed labeling (per 14-day post approval requirement)	n/a	TBA	closed	Yes (0046, 11/11/11)
80	Pacira	RA	eCTD	11/17/2011	regional	Pacira sends final patent certification	n/a	TBA	closed	Yes (0047, 11/17/11)
81	Pacira	RA	eCTD	11/17/2011	regional	Pacira submits final SPL for dailymed listing	n/a	TBA	closed	Yes (0048, 11/17/11)

EXHIBIT R

PCIRA.000GEN EXHIBIT R

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent	:	SANKARAM, Mantripragada et al.
App. No.	:	09/045,236
Filed	:	March 20, 1998
Patent No.	:	6,132,766
Issue date:	:	October 17, 2000
For	:	MULTIVESICULAR LIPOSOMES WITH CONTROLLED RELEASE OF ENCAPSULATED BIOLOGICALLY ACTIVE SUBSTANCES

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.740(b) FOR EXTENSION OF PATENT TERM

I, Mallary K. de Merlier, patent attorney with the firm of Knobbe, Martens, Olson & Bear, LLP, and registered to practice before the Patent and Trademark Office, have Power of Attorney to act on behalf of the assignee, Pacira Pharmaceuticals, Inc., the owner of the entire right, title and interest in U.S. Patent No. 6,132,766, in executing this Declaration and attached application for extension of patent term.

I hereby declare the following:

(1) I have reviewed and understand the contents of the application being submitted pursuant to 37 C.F.R. §1.740;

(2) I believe that the patent is subject to extension pursuant to §1.710;

(3) I believe an extension of the length claimed is justified under 35 U.S.C. §156 and the applicable regulations; and

(4) I believe that the patent for which extension is sought meets the conditions for extension of a patent as set forth in §1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the U.S. Code and that such willful, false statements may jeopardize the validation of the application or any extension issued thereon.

Date: December 22, 2011

Mallary K. de Merlier
Registration No. 51,609
Attorney of Record

12466977
122011